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Master Thesis

肝細胞癌的初級、次級和三級預防策略之成本效益分析

Cost-effectiveness analysis for the primary, secondary, and tertiary prevention of hepatocellular carcinoma

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中文摘要

前言：

儘管台灣在過去三十年中，透過初級至三級預防性策略降低肝細胞癌發生，已有顯著成效，然而如何結合不同層級的預防策略，應用族群和個人層次之預防策略以獲得最佳效果是目前肝癌防治相當有趣的議題。尤其當經濟觀點評估應用於施行全面性新生兒B型肝炎疫苗施打後及對於未接種疫苗的出生世代結合腹部超音波篩檢與抗病毒治療之議題，截至目前為止尚未有相關研究進行深入探討。本研究目的如下：

(1) 利用台灣實證資料，呈現並探討全面性接種B型肝炎病疫苗、全民健康保險實施（NHI）、腹部超音檢查及抗病毒治療之後，以長期資料探討台灣肝癌發生率、死亡率和致死率之時間趨勢之經驗。

(2) 在無任何介入模式下，發展肝癌自然病史模型（從病毒感染、健康復原、帶原者及慢性肝病）及肝癌預後模式進行經濟評估之比較。

(3) 發展一系列馬可夫決策模型，以肝癌疾病自然史為基礎，包含不同介入性策略及肝炎病毒感染、慢性肝病和肝癌之後續病程變化及預後。

(4) 根據本研究目的(2)所呈現台灣目前情況下之肝炎病毒感染盛行率和發生率以及肝癌發生率等參數，以模擬該人口之假設性世代，進一步以(1)中呈現各種不同介入性計畫進行效益和效用評估。

(5) 針對合併不同介入性計畫之不同策略組合進行經濟評估，包括全面性B型肝炎疫苗接種、大規模腹部超音波篩檢及抗病毒治療等。

(6) 根據肝炎患者對於抗病毒治療後之病毒反應（sustained virological response ,SVR）不同而提供個人化監控計畫進行經濟評估。

(7) 比較肝癌治療之射頻燒灼術(Radiofrequency Ablation, RFA)及外科切除手術之成本效益分析。

材料與方法：

本研究透過整合B型肝炎疫苗接種和抗病毒治療之初級預防性策略、次級預

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防之腹部超音波篩檢及三級預防性策略，提出了將上述若干預防方案整合為一的整體經濟評價之總體框架。從 1984 年到 2013 年，藉由使用生命統計資料來闡明經由各種預防措施相對應的符合條件的四個年齡段出生世代，所產生肝癌時間趨勢流行病學。利用波以松回歸模型估計相對應介入措施的效益。

根據肝癌疾病自然史，本研究從易感受性人口，考量孕婦垂直傳播引起的Ｂ型肝炎感染、恢復或帶原者、慢性肝病、肝細胞癌、補償性和失代償性肝硬化，直到死亡作為無預防性介入組。利用馬可夫決策模型模擬各種不同組合介入措施之成本效益分析，包括全面性 B 型肝炎疫苗接種、抗病毒治療和腹部超音波篩檢。對於具有 SVR 的病患也進行個人化監控計畫的經濟評估。此外，也進行肝癌接受 RFA 手術與切除手術的成本效益分析比較。

結果：

從 2000 年以來，肝癌的整體發生率和死亡率已經開始下降。自 1985 年以來，個案致死率持續下降，尤其在 2000 年後，即全民健康保險（NHI）實施五年後，下降幅度更加明顯。根據各類與介入計畫接觸的出生世代，將年齡分為四類：<30 歲、30-49 歲、50- 69 歲、70 歲以上，我們發現除了老年人（70 歲以上）以外，各類年齡層的肝癌發生率呈下降趨勢。

就單一模式的初級和次級預防的效用和效益來看，普遍接種疫苗有效降低 88％（95％CI：85％，90％）肝臟疾病和因肝癌所導致死亡，亦導致所有個案的死亡比例降低 15％（95％CI： 11％，20％）。透過抗病毒治療可避免 16％（95％CI：8％，25％）因 HBV 所造成肝癌死亡、可避免 2％（95％CI：0.2％，5.6％）因 HCV 所造成肝癌死亡和可避免 18％（95％CI：10％，23％）因 HBV 和 HCV 所造成肝癌死亡。大規模腹部超音波篩檢，相較於沒有介入組，可減少約 14％（95％CI：6％，20％）的肝癌死亡個案。相較於沒有介入組，合併使用全面免疫接種與抗病毒治療、大規模篩檢、兩者皆使用者則分別減少約 90％（95％CI：88％，91％）、89％（95％CI：87％，91％）和 91％（95％CI：86％，95％）肝癌死亡。若以全面性疫苗接種策略作為參考組，合併使用全面免疫接種與抗病毒治療、大規模篩檢、前兩者皆使用者，其分別可以降低 17％（95％CI：7％，28％），13％（95％

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CI：3%，23%）和 29%（95%CI：-14%，59%）肝癌死亡。

成本效益分析結果顯示，單一模式的全面性免疫接種較無介入措施組顯著優勢（節約成本），達成本效益的機率是 100%。任何預防性介入策略與疫苗接種組合，較無介入措施組為優勢（節省成本）。單一模式 HBV 和 HCV 的抗病毒治療、篩檢介入策略，相較於無介入措施組的增加成本效益比（ICER）分別為 5,137 美元（95%CI：672 美元，22,245 美元）和 3,323 美元（95%CI： - 1,339 美元，16,002 美元）。

合併使用全面性疫苗接種與 HBV 和 HCV 的抗病毒治療、篩檢策略、前兩者皆使用者相較於全面疫苗接種的 ICER 分別為 4,633 美元（95%CI：- 33,414 美元，34,875 美元），11,668 美元（95%CI：- 58,164 美元，31,715 美元）和 9,102 美元(95%CI：- 103,320 美元，33,628 美元)。然而，在考量參數的不確定性下，成本效益的機率達到了 60%-70%。針對使用干擾素治療後之持續性病毒反應的低風險患者，藉由個人化策略延長監測的間隔可以將降低 60%成本，而不損害生命年。成本效益分析結果顯示，手術成本較低（1155.37 美元），且獲得了 0.6231 的壽命年，這說明手術比 RFA 為優勢（節省成本）。

結論：

本論文透過流行病學時間趨勢的實證證據，評估了各種預防策略降低肝癌發生率和死亡率的實證效益。進一步針對各種介入措施的不同組合，進行了系統性的經濟評估，評估結果顯示全面施打疫苗策略，即使與各種抗病毒治療組合，也是節省成本。另外，對於進行抗病毒治療後的 SVR 患者，可以提供個人化的最佳監測策略可行性相當高。在考慮各種介入措施的不同組合下，進行系統的經濟評估，對於與台灣有類似肝炎病毒感染情況相同的國家是非常有幫助的。

關鍵字：肝細胞癌、疫苗、篩檢、抗病毒治療、成本效益分析

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Abstract

Background Despite much effort made to reduce hepatocellular carcinoma (HCC) over past three decades from primary to tertiary prevention in Taiwan, how to combine different levels of preventive strategies to reach the optimal benefit become an interesting subject on the prevention of HCC at population level and individual level. This is particularly relevant to the underpinnings of economic appraisal when the entire population has been intervened by universal hepatitis B vaccination administered to neonates and screening for HCC with abdominal ultrasonography together with the advent of anti-viral therapy for birth cohorts without being vaccinated. However, such a subject has been never addressed.

Aims The aims of this thesis are to

(1) provide empirical evidence on time trends of incidence, case-fatality, and mortality of HCC after introduction of universal vaccination against hepatitis B virus infection, national health insurance (NHI), abdominal sonography screening, and anti-viral therapy based on Taiwan experiences;

(2) develop a natural history (from infection, recovery, carrier, and chronic liver disease) and prognosis of HCC model for the comparator of the following economic appraisal in the absence of intervention program;

(3) develop a series of Markov decision model for accommodating how these intervention programs alter the baseline disease natural history and also subsequent prognosis of the sequelae of hepatitis virus infection, chronic liver disease, and HCC;

(4) evaluate the efficacy and effectiveness of various intervention programs indicated in (1) through the simulation of a hypothetical cohort with the make-ups of

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demographic features, the prevalence and incidence rate of hepatitis virus infection, and incidence of HCC similar to Taiwanese scenario based on (2) ;

(5) do economic appraisal of various combinations of intervention programs including universal vaccination, mass screening with abdominal sonography, and anti-viral therapy.

(6) do economic appraisal of personalized surveillance schedule for those sustained virological response (SVR);

(7) compare cost-effectiveness of Radiofrequency Tumor Ablation (RFA) surgery and resected surgery;

Materials and Methods

Overall framework of economic appraisal of intervention program of HCC from primary prevention with vaccination and anti-viral therapy, secondary prevention with abdominal sonography screening, and tertiary prevention has been proposed to unify each intervention program as a whole. Time-trend epidemiology of HCC by four age bands corresponding to the eligible birth cohort with various intervention was elucidated by using vital statistics since 1984 until 2013. Poisson regression model was used to model the effectiveness of the corresponding intervention programs.

The disease natural history of HCC was develop from susceptible population, hepatitis B virus infection considering maternal vertical transmission, recovery, carrier, chronic liver disease, hepatocellular carcinoma (HCC), compensated and decompensated liver cirrhosis and until death to represent no intervention group. An analytical Markov decision model was used to model cost and effectiveness analysis of various combinations of intervention including universal vaccination, anti-viral therapy, and abdominal ultrasonography screening. Economic appraisal was also performed for

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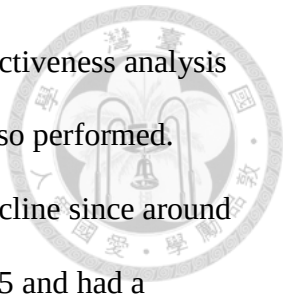


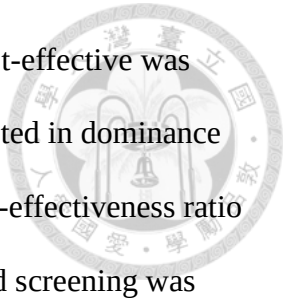
personalized surveillance schedule for those who had SVR. Cost-effectiveness analysis for the comparison between RFA surgery and resected surgery was also performed.

Results The overall incidence and mortality of HCC has started to decline since around 2000. Time trends in case-fatality has consistently declined since 1985 and had a dramatic decrease after 2000, five years after the introduction of national health insurance (NHI). By classifying age band into four categories, < 30 year, 30-49 years, 50-69 years, and 70+ years in accordance with the implementation of various available intervention methods for eligible birth cohorts, we found all the time trends of incidence of HCC except old age group (70+ years) have shown a declining trend due to each category of birth cohort experiencing each corresponding intervention program.

For the efficacy and effectiveness of primary and secondary intervention with single modality, universal vaccination contributed to 88% (95% CI: 85%, 90%) reduction of liver diseases and deaths from HCC, which led to 15% (95% CI: 11%, 20%) reduction of all-cause of death compared with no intervention. The anti-viral therapy was associated with 16% (95% CI: 8%, 25%), 2% (95% CI: 0.2%, 5.6%), and 18% (95% CI: 10%, 23%) HCC death averted due to HBV, HCV, and both, respectively. Abdominal ultrasonography mass screening, conferred 14% (95% CI: 6%, 20%) reduction of death from HCC. The combined use of universal vaccination with anti-viral therapy, mass screening, and both made contribution to 90% (95% CI: 88%, 91%), 89% (95% CI:87%, 91%), and 91% (95% CI: 86%, 95%) reduction of death from HCC, respectively, compared to no intervention. The corresponding figures were 17% (95% CI: 7%, 28%), 13% (95% CI: 3%, 23%), and 29% (95% CI: -14%, 59%) compared with the scenario of vaccination taken as the reference group.

The cost-effectiveness analysis shows that single modality of universal vaccination

doi:10.6342/NTU201703133



dominated no intervention (cost-saving). The probability of being cost-effective was 100%. Even any prevention strategy combined with vaccination resulted in dominance (cost-saving) as compared with no intervention. The incremental cost-effectiveness ratio (ICER) of single modality of anti-viral therapy of HBV and HCV, and screening was $5,137 (95% CI: $672, $22,245), and $3,323 (95% CI: -$1,339, $16,002), respectively, than no intervention. The ICERs for the combined used of vaccination with anti-viral therapy of HBV and HCV, screening, and both were $4,633 (95% CI: -$33,414, $34,875), $11,668 (95% CI: -$58,164, $31,715), and $9,102 (95% CI: -$103,320, $33,628), respectively, than universal vaccination only. However, the probability of them reached plateau to 60%-70% given the uncertainty of parameters. A personalized strategy with prolonged surveillance intervals for low risk patients with sustained virological response after interferon could reduce cost by 60% without compromise of the life-year gained. The cost-effectiveness analysis suggests that surgery cost less ($1155.37) but earned 0.6231 life-years, which suggests surgery dominated RFA (cost-saving).

Conclusions This thesis has evaluated the effectiveness of reducing incidence and mortality of HCC by various intervention programs by using the empirical data on time-trend of epidemiology. Systematic economic appraisal for evaluation of various combinations of intervention programs have been done to show universal vaccination even in the combination with anti-viral therapy was always cost-saving screening. Optimal personalized surveillance for those with SVR seems available after the administration of anti-viral therapy. Such systematic economic appraisal is very helpful for the country with the same scenario of hepatitis virus infection in Taiwan when various combinations of intervention programs have been considered.

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Keywords：hepatocellular carcinoma , vaccination , screening, anti-viral therapy , Cost-effectiveness analysis .

doi:10.6342/NTU201703133

Contents

doi:10.6342/NTU201703133

doi:10.6342/NTU201703133

doi:10.6342/NTU201703133

LIST OF FIGURES

doi:10.6342/NTU201703133

doi:10.6342/NTU201703133

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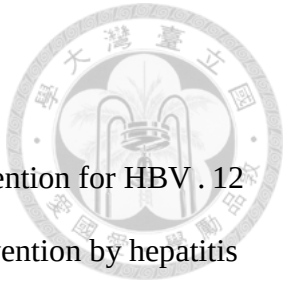

LIST OF TABLES

doi:10.6342/NTU201703133

Chaper 1 Introduction

1.1 Issues of epidemiological profiles of HCC

Hepatocellular carcinoma (HCC) is the leading cause of death, accounting for more than 780,000 tolls worldwide. The following figures show the time trend of age-standardized incidence and mortality of HCC. It indicated an increasing trend for both incidence. However, as vaccination, screening and anti-viral therapy have applied to different birth cohorts and periods, examining the overall incidence and mortality is not justified to make inference about the effectiveness of these intervention programs. Age-specific curves in commensurate with birth cohorts eligible for receiving different intervention programs is therefore worthy of being investigated.

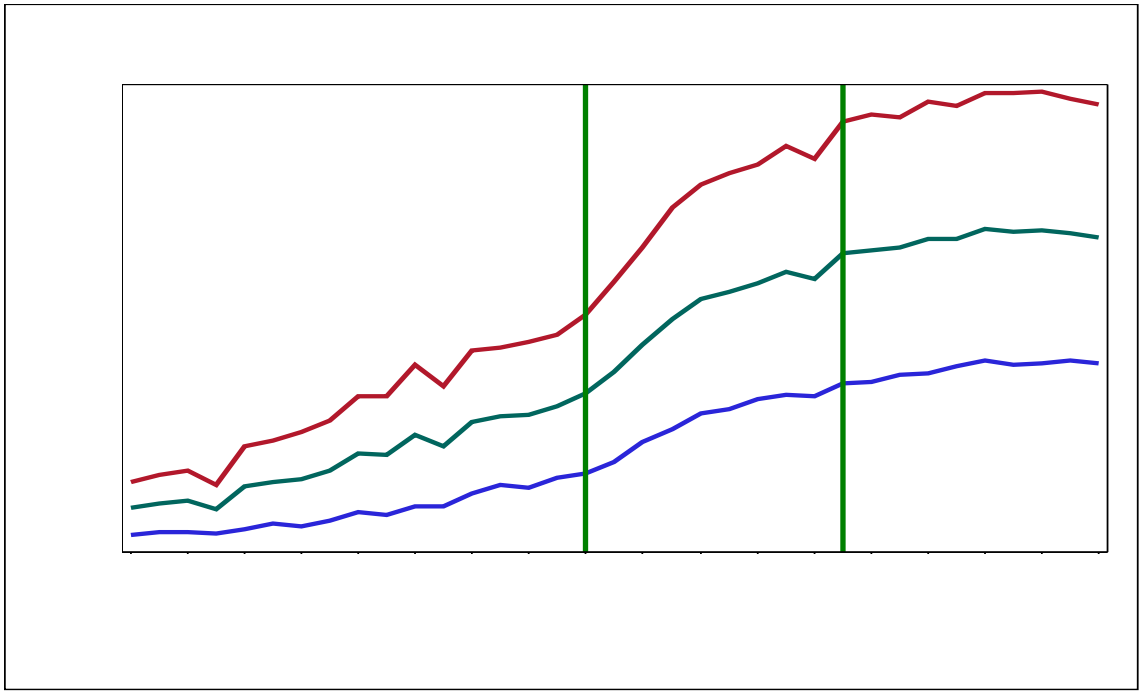

Figure 1. 1.The age-standardized incidence rate of HCC

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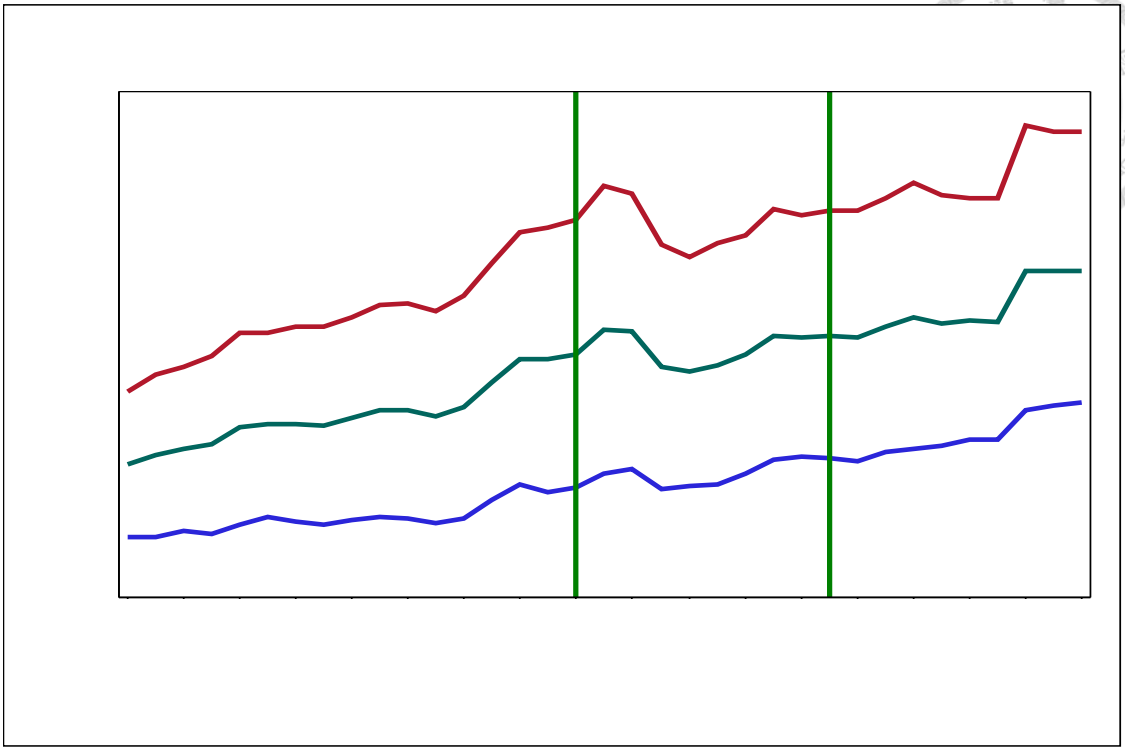

Figure 1. 2 The age-standardized mortality rate of HCC

1.2 Evolution of intervention program for HCC

In order to reduce its mortality, different levels of prevention at population, community, institution, and individual levels have been adopted since 1980s. The classical population-based primary prevention program is the administration of universal hepatitis B vaccination according to successive eligible birth cohorts that had been implemented in Taiwan since 1984. The evidence on a decline of HCC incidence in childhood live cancer has been demonstrated after the implementation of universal HBV vaccination (Chang et al, 1997).

Although universal vaccination is an efficient approach to preventing deaths from HCC, birth cohorts that had not been stood a chance of being vaccinated are still

doi:10.6342/NTU201703133

susceptible to the risk for HCC through virus-related, particularly hepatitis B and C virus infection, and non-virus-related pathways such as NASH-related cirrhosis. Various screening strategies such as two-stage approach using biomarkers in combination with abdominal ultrasonography and universal approach with abdominal ultrasonography were therefore offered for these cohorts that has not been vaccinated (Yeh et al, 2014).

Due to early detection of HCC, treatment modalities for HCC have also evolved from only surgery for resectable tumor to RFA or TACE and PEI. This evolution is in parallel with the advent of new adjuvant therapy and target therapies (Poon et al, 2004; Lin et al, 2013). More importantly, the evolution of treatments and therapies have not only lengthened the survival but also improved the quality of life.

While screening for HCC is implemented it identifies latent but potential of being susceptible to HCC such as HBV and HCV carriers. To reduce the incidence of HCC among these two high-risk groups, anti-viral therapies for treating hepatitis B and C patients have been proposed since early 2000s. Since then, a series of novel drugs on this part have been in tandem.

1.3 Economic appraisal of different intervention programs

The recently proposed value-based health care indicates the rationale for doing economic appraisal for different levels of prevention. Since the target population of intervention varies with different cohorts and age groups, cost and effectiveness would be very heterogeneous. The results of cost-effectiveness analysis across different interventions are therefore worthy of being compared if they have the effectiveness of outcome (such as mortality reduction) in common.

More importantly, although economic appraisal for each intervention program has been done very few studies on economic appraisal have been conducted to address

doi:10.6342/NTU201703133

the combination of different intervention programs for prevention of HCC. For example, what are the dynamic profiles of cost-effectiveness when universal vaccination administered to neonates is combined with abdominal ultrasonography? The similar scenarios are also applied to the combination of universal vaccination with anti-viral therapy or the combination of three preventive strategies. Providing such a kind of information on economic appraisal is particularly important for some south Asian countries where prevalence and incidence of HBV and HCV infection are similar to Taiwan but have not been administered with any preventive strategy.

1.4 Systematic analysis from time trend epidemiologic assessment to economic evaluation

As indicated earlier, universal vaccination against hepatitis B vaccination, two-stage screening and mass screening with abdominal sonography, and different treatments and therapies have been successfully implemented since 1984 in Taiwan. Different levels of intervention may affect different subsequent outcomes that are related to HCC mortality. Universal vaccination reduces the risk of being susceptible to HBV infection. Anti-viral therapy prevents the occurrence of HCC. Screening with abdominal ultrasonography may reduce the risk of developing advanced HCC through early detection, leading to the reduction of HCC mortality. Different modalities of treatment and therapy, particularly after the introduction of national health insurance, may affect the recurrence of HCC and also HCC mortality. Providing time trends of incidence and case-fatality of HCC throws light on the contribution of various interventions to explain time trends of mortality from HCC. Evidence based on Taiwan experience provides a good opportunity for illustrating the effectiveness of various intervention programs. In addition to effectiveness, since different intervention

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programs involve various costs systematic economic evaluation of primary, secondary, and tertiary prevention of HCC is therefore of great interest to health policy-makers given the limited resources. Due to limited time and space, this thesis here is focused on the combination of primary and secondary prevention while the comparisons of different treatments and therapies are not addressed.

Objectives

The aims of this thesis are to

(1) provide empirical evidence on time trends of incidence, case-fatality, and mortality of HCC after introduction of universal vaccination against hepatitis B virus infection, national health insurance (NHI), abdominal sonography screening, and anti-viral therapy based on Taiwan experiences;

(2) develop a natural history (from infection, recovery, carrier, and chronic liver disease) and prognosis of HCC model for the comparator of the following economic appraisal in the absence of intervention program;

(3) develop a series of Markov decision model for accommodating how these intervention programs alter the baseline disease natural history and also subsequent prognosis of the sequelae of hepatitis virus infection, chronic liver disease, and HCC;

(4) evaluate the efficacy and effectiveness of various intervention programs indicated in (1) through the simulation of a hypothetical cohort with the make-ups of demographic features, the prevalence and incidence rate of hepatitis virus infection, and incidence of HCC similar to Taiwanese scenario based on (2) ;

(5) do economic appraisal of various combinations of intervention programs including universal vaccination, mass screening with abdominal sonography, and anti-viral therapy.

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Chapter 2 Literature Review

2.1 Primary intervention by HBV vaccination

The immunized vaccination of HBV has been developed in 1980 successfully. The HBV transmission types and prevalence rates of HBV carriers are different from country by country, such as vertical transmission in Asian countries with high prevalence rate of HBV carriers and horizontal transmission in western countries with low HBV carriers. Therefore, the background status and characteristics should be taken into account for the policy making of HBV vaccination. So far, some cost-effectiveness analysis has been published according to the variant situation.

Targeted at infants

-Targeted on newborn vaccination in high endemic area

The prevalence rate and transmission rate are high in Taiwan due to vertical transmission from maternal HBV carriers. Before two decades ago, the significant reduction of HCC incidence and HBV infection in children has been affected by universal vaccination program in Taiwan based on the high prevalence arte of HBV carriers (15-20%) (Chang et al., 1997). According to this first universal vaccination program in the world, Hung and Chen conducted the probabilistic cost-effectiveness analysis to evaluate the economic appraisal based on Taiwanese parameters. Taking the cost and burden of long-term sequent medical care and surveillance, both societal and health care perspectives were proposed to explore. The universal vaccination program not only could reduce 86% of the HCC incidence and death on effectiveness which caused by HBV infection, but also be cost-saving regardless of societal and health care perspectives. This study demonstrated the cost-saving strategy preventing from HCC

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incidence and mortality in high prevalence rates of HBV surface antigen and HBeAg positive endemic area (Hung and Chen, 2009). In 2012, Chen et al. compared the different combination of HBsAg and HBeAg test and HBIG treatment for mother HBeAg status, compared with universal HBV vaccination, the results show the universal vaccination combined HBIG treatment is cost-effective. However, the universal vaccination is preferable when the health resource is limited (Chen et al., 2012).

The prophylaxis treatment of Lamivudine inhibits was developed in recent decade to suppress the HBV replication for carriers and reduce the complications from HBV infection, which also gave the treatment for pregnant women before delivery to reduce the vertical transmission. In 2011, Hung and Chen evaluated the economic appraisal for Lamivudine treatment combining vaccine and HBIG on infant compared with existing strategy of universal vaccine and HBIG. Considering the quality of life year gained and averted acute infection, the Lamivudine prophylactic treatment was suggested cost-effectiveness and dominated existing policy. Given on US$20,000 of willing-to-pay threshold, the acceptability curve shows 94% probability of being cost-effectiveness (Hung and Chen, 2011).

In China, the hepatitis B carrier rate is high endemic and the majority is due to maternal vertical transmission. In 2013, Lu et al. conducted the cost-effectiveness analysis of universal vaccination with long-term follow-up scenario to incorporate the cost of medical care which covered by societal perspective and health care provider perspective only approaches, compared with no vaccination. The coverage rate of birth dose of hepatitis B vaccine delivered to new born within 24 hours was also taken into account due to the variation in China. Based on simulation with 10 million infants, the

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results show the cost was US$620,000 per QALY for both perspectives and saved US$1,429,000,000 and US$1,059,000,000 for societal perspective and health care provider perspective, respectively. This study strongly supported that the universal HBV vaccine not only can save the life , but also save the cost in medical care and society as well (Lu et al., 2013).

-Catch-up HBV vaccine for children and adolescent in high endemic area

Among the high endemic HBV infection area, there are still large proportion of children and adults not protected by HBV vaccination due to the vaccination policy initiated from newborn. Therefore, there is still have room to discuss about the catch-up policy for children or adults to last the protection of HBV infection from liver disease and liver cancer attack in long-life. In 2010, Hutton et al. proposed the cost-effectiveness analysis for nationwide hepatitis B catch-up vaccination among children and adolescents who were missed from newborn vaccination policy in China using the societal perspective. Given on the 70% compliance rate of vaccination and 95% protection rate with three-dose vaccine, the hepatitis B catch-up vaccination is cost-saving regardless of age groups. Therefore, this experience and CEA analysis provides the important message for the HBV catch-up vaccination benefit for adolescent aged under 19 (Hutton et al., 2010).

-Targeted on newborn vaccination in low infection rate area

Compared with the HBV infection rate in Asian countries, the HBV infection rate in Ireland is lower but mixed with high-risk subpopulation. The strategies of high-risk selective approach and universal HBV vaccination combined existing other vaccination

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for all infants' universal strategy were evaluated by cost-effectiveness based on Ireland status. The administrative fee for vaccination would be reduced due to combine five existing children vaccination (diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae) in Ireland during the universal vaccination strategy. Based on the acute infection rate of 8.4 per 100,000, the result shows the incremental cost-effectiveness of life-year gained on universal strategy was Euro 37,018 given on the Euro 29 per dose of vaccination compared with high-risk selective population. But, the incremental cost-effectiveness was sensitive to the cost of HBV vaccination price (Tilson et al., 2007).

The HBV infection rate is quite low in UK, but some high-risk population transmitted through vertical and horizontal pathway; therefore, the HBV vaccination for infant and adolescent was suggested in UK. However, for those high-risk group should be identified by screening, but the compliance rate for vaccination would be expected lower. So, the economic evaluation appraisal was suggested by Siddiqui et al. in 2011. The study found that universal infant vaccination could reduce more HBV-related morbidity and mortality compared with universal adolescent vaccination (81% vs. 46%). But, both strategies would not be suggested cost-effectiveness. However, the lower price of vaccination would make the cost-effectiveness on universal program of HBV vaccination (Siddiqui et al., 2011).

Targeted at adults

-High risk group of diabetes

Regarding the transmission of HBV in USA, the major HBV infection are caused by horizontal blood contact, e.g. employee in hospital, dialysis, drug injection, sexual

doi:10.6342/NTU201703133

and family contact. Those diabetes patients have been recognized as high risk group of HBV infection due to misusing contaminant blood monitor/equipment, high likelihood of dialysis, and kidney transplantation etc. In the light of incidence and prevalence rate of diabetes are increasing in the world, the health policy makers are rethinking whether we should give the HBV vaccination in adulthood or not. In 2013, Hoerger et al. conducted the decision-analytic Markov model to evaluate the cost-effectiveness analysis for HBV vaccination on diabetes adults. Based on the aged 20-59 population with diagnosed diabetes, using the three doses in three schedules for all subjects and considering the reduction from acute and chronic hepatitis caused liver cirrhosis, HCC, and transplantation, the results demonstrated the cost-effectiveness for aged 20-59 diabetes with US$75094/per QULY, but not for diabetes aged more than 60 (US$2,760,753/ per QALY) (Hoerger et al., 2013).

HBV vaccination was developed and designed for three-dose series over 6 months, but the efficacy of seroprotection is dependent on the complete schedule or not. The new vaccination for HBV-HEPLISAV^{TM} is developed for adults that contains recombinant HBV surface antigen with phosphorothioate oligonucleotide which can achieve 96% seroprotection after two doses only (only 20-30% seroprotection after two doses of existing vaccine). Among those high-risk of HBV infection adults, i.e. diabetes, CKD, ESRD, healthcare workers, and travelers, HEPLISAV^{TM} vaccine shows the cost-effectiveness with ICER<25000 and demonstrated the dominant cost-saving, especially for both CKD and ESRD. This result indicated the new HEPLISAV^{TM} is promising for HBV vaccination for high-risk adults (Kuan et l., 2013).

-High risk of HIV counseling and testing sites

Those who of having drug users, Man-to-Man sexual behavior, or multiple sexual

doi:10.6342/NTU201703133

partners are also high-risk of HBV infection through horizontal transmission because the pathway of HBV infection is quite similar to HIV. In 2006, Kim et al. proposed the cost-effectiveness analysis for the HBV vaccination or screening strategies to prevent hepatitis B among this high-risk population, including HIV counseling and testing sites and sexually transmitted disease (STD) clinics. Compared with no intervention, the strategies included (A) routine vaccination without screening for prior immunity or infection, (B) screening for antibody to hepatitis B core antigen and HBV marker of current or past infection with initial dose, (C) screening combined vaccination based on screening results. The results reported the routine vaccination policy would be effective and cost-effectiveness for those high-risk subpopulation, including HIV counseling and testing sites and STD clinics, they demonstrated the cost would be US$4400 and US$3500 per QALY or life-year gained for HIV counseling and testing sites and STD clinics, respectively (Kim et al., 2006).

In 2008, Rain et al. investigated the vaccine combined hepatitis A and B compared with HBV vaccine only using cost-effectiveness analysis, the incremental cost-effectiveness per QALY gained of combining hepatitis A/B were US$44,000, US$88,000, US$132,000, US$162,000 for incidence rates of 10.3, 6.17, 4.2, and 3.0, respectively. This indicates that cost would be highly dependent on the background incidence rates of HBV infection (Rain et al., 2008).

For those primary intervention using HBV vaccination, for infant or high-risk adults, were summarized in the following Table 2.1. The different strategies and monitoring indicators were also demonstrated in table. The incremental cost-effectiveness was conducted to present the comparison among those strategies that were proposed by each study, see Table 2.1.

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Table 2. 1 Summary of cost-effectiveness analysis for primary intervention for HBV

Author	Year	Study population	Method/Model	Study design/Strategies	Outcome
Kim et al.	2006	Clients attending HIV CTSs/ United States	Decision model、Markov model of natural history of HBV infection	①Routine vaccination ②Screening with initial dose ③Screening and vaccination vs. no-intervention	Routine vaccination was more cost-effective than either screening strategy.
Tilson et al.	2007	Infants/Ireland	Decision-analytic Markov model	universal vs. selective hepatitis B vaccination (high-risk infants)	The incremental cost effectiveness of the universal compared with the selective vaccination program me is €37018/life years gained (LYG)
Rein and Weinbaum	2008	High-risk heterosexuals / United States	Markov model	universal use of combination hepatitis A/B vaccination vs. universal use of combination hepatitis B vaccination alone	The incremental cost-effectiveness of combination vaccine was $120,000 per QALY gained.
Hung and Chen	2009	Newborns / Taiwan	Markov Decision analysis、probabilistic cost-effective analysis using Monte Carlo simulation	Universal vaccination vs. no-vaccination	Vaccination reduce hepatocellular carcinoma cases and deaths was approximately 86%. and the average life years gained per subject was 3.9. (less cost and more effectiveness).
Fischinger et al.	2010	Blood donors /Germany	A survey-based cost-benefit analysis	Strategy ①A2：A1+HBV NAT(minipool) ②A3：A1+HBV NAT(individual) ③B1：anti-HBs titre +time dependent booster vaccination ④B2：anti-HBs titre +titre dependent booster vaccination ⑤B3=B2+A1 vs. A1=HBs+anti-HBc detection	Strategy B1 and B2 were cost-saving compared to A1.
Hutton et al.	2010	Children and adolescents aged 1 to 19 years /China	Markov model of disease progression	catch-up vaccination vs. the status quo with current levels of vaccination coverage.	Catch-up vaccination is cost-saving

doi:10.6342/NTU201703133

Author	Year	Study population	Method/Model	Study design/Strategies	Outcome
Siddiqui et al.	2010	Infants and adolescents/UK	HBV Markov model	①Universal infant vaccination ②universal adolescent vaccination ③ selective infant HBV vaccination (intermediate and high-risk ethnic populations)	A universal infant, universal adolescent or a selective infant vaccination programme would not be considered cost-effective at current vaccine prices.
Hung and Chen	2011	Newborns / Taiwan	Markov Decision Framework、Directed acyclic graphic(DAG) model with a Bayesian random-effect logistic regression model、probabilistic sensitivity analysis	Pregnant women use lamivudine (plus vaccine + HBIG given to infant) vs. Vaccine + HBIG given to infant	Supplemental lamivudine use gained an additional 0.0024 QALYs and averted 0.23 acute infections per birth compared with the routine active-passive immunization without lamivudine.
Chen et al.	2013	Neonates of carrier mothers/ Taiwan	Decision-analytic model	① Strategy S: universal vaccination plus maternal screening for HBsAg, HBIG given for neonates born to HBsAg(+) mothers. ②Strategy E: universal vaccination plus maternal screening for HBeAg, HBIG given for neonates born to HBeAg(+) mothers. ③Strategy S&E: universal vaccination plus maternal screening for HBsAg followed by screening for HBeAg among HBsAg(+), HBIG given for neonates born to HBeAg(+) carrier mothers, and HBIG optional for neonates of HBeAg(-) HBsAg(+) mothers. vs. Strategy V: universal vaccination for all	The most aggressive strategy for augmenting vaccination, HBIG for all neonates with HBsAg(+) mothers (strategy S) averted the most infections, followed by strategy S&E and strategy E, which primarily cover neonates born to the subset of carrier mothers who are also HBeAg(+).

doi:10.6342/NTU201703133

Author	Year	Study population	Method/Model	Study design/Strategies	Outcome
				neonates, no routine screening or HBIG treatment.	
Hoerger et al.	2013	Unvaccinated adults with diagnosed diabetes /U.S.	Decision-analytic Markov model	vaccination vs. no vaccination	Hepatitis B vaccination for adults with diabetes 20–59 years of age is modestly cost-effective
Kuan et al.	2013	Selected high-risk adult populations (patients with CKD or ESRD, healthcare workers, travelers and diabetic patients) /USA	Markov model of disease progression	HEPLISAV^{TM} vs. Engerix-B	For patients with CKD and ESRD , HEPLISAV is cost-saving . In the healthcare workers, travelers and diabetic patients, HEPLISAV is cost-effective option compared with Engerix-B with ICERs below $25000.
Lu et al.	2013	Infants/China	Decision tree、Markov model	Universal newborn vaccination comprising a timely birth dose (HepB1) with a three-dose vaccination(HepB3) vs.no-vaccination	Compared with no vaccination, universal newborn vaccination would prevent new HBV infections and long-term sequelae. It also saved life years, improved quality of life and reduced costs of care.
Hung et al.	2014	Newborns / Taiwan	Markov cycle decision tree by conjoining the temporal natural history of HBV infection	① Universal vaccination +HBIG ② Universal vaccination +HBIG +lamivudine vs. no-vaccination	Both preventive strategies were cost-saving, yielding the negative value of incremental cost-effectiveness ratio, compared with the baseline group (no intervention).

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2.2 Secondary prevention for HCC by hepatitis B screening

The HBV infection is the major cause for the liver disease and hepatocellular carcinoma due to the chronological infection and pathological change, like liver compensated or decompensated cirrhosis and HCC; therefore, those characteristics will be leading to the burden of care and medical expenditure, especially for those endemic HBV infection areas. Besides those vaccination policy, however, there are still have wide range of population who did not covered and protected by vaccination immunized intervention. Some surveillance and screening strategies were proposed to rescue those burdens for societal impact, but the effectiveness and economic scale would be highly dependent on the prevalence rate of HBV, adequate healthcare system, and compliance rate of surveillance, etc. So far, there were some scientific reports based on economic evaluation have been demonstrated, see below.

Targeted on high prevalence rate of HBV infection

In Iran, the prevalence of HBV carriers is about 1.3% to 8.69% in general population, but HBV is leading to 70-80% of chronic hepatitis cases in Iran. To reduce the prevalence rate of HBV infection, the policy on premarriage can be reduce the vertical and horizontal transmission pathways. Therefore, the economic evaluation with health care and societal perspectives were proposed to get the optimal strategy. The strategies included (a)HBsAg screening for those couples, the HBIG, vaccination, and condom were provided for those one of HBsAg, (b)HBsAg screening as (a), in addition to provide HBcAb. Using the observational outcome as number of chronic HBV, the strategy (b) shows slight cheaper than (a). Both strategies were cost-saving to prevent chronic liver disease (Adibi et al., 2004).

In Gambia, the HBV infection rate is high and still no vaccination policy for those

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areas, but there is no antiviral therapy for those carriers. To reduce the impact on HBV-related disease in Gambia, the screening and treatment with antiviral therapy was proposed to evaluate by economic appraisal. In 2016, Nayagam et al. conducted the economic evaluation of community-based HBsAg rapid screening combining subsequent antiviral therapy compared with current policy with no screening and treatment. Those parameters were conducted from PROLIFIC study, which assessed the epidemiological status in Gambia. Given on the no resistance of tenofovir treatment and completely adherent to treatment, the community-based screening and treatment has incremental cost-effectiveness ratio of US$511 per QALY gained and US$540 per DALY averted compared with current policy. Using the probabilistic sensitivity analysis, the incremental cost-effectiveness ratio was increased by decreasing of prevalence rate of HBsAg positive (Nayagam, et al., 2016).

Targeted on high-risk population but in low prevalence area

In western countries, people who immigrated from Asian countries have high HBV carrier rate compared with local residents. Identifying those high-risk group and giving the treatment are the first task for prevention of HCC and HBV-related disease. In 2007, Hutton et al. conducted the economic evaluation to propose the optimal strategy for HBV carriers medical care in American. Compared with no any intervention, there were four strategies, included (a) universal vaccination, (b)screen+treat, (c)screen+treat+vaccinate, and (d)screen+treat, and ring vaccinate, to evaluate the best QALY gained using the societal perspective. Given on 100% for blood examination and 70% compliance rate for intervention, Probabilistic sensitivity analysis shows both strategies of screen+treat and screen+treat,and ring vaccinate are similar and cost-effective. The incremental cost-effectiveness ratio was US$36,088 for screen+treat

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compared with none and US$39,903 for screen+treat,and ring vaccinate compared with screen+treat. The probabilities were 82% and 97% of being incremental cost-effectiveness of less than US$50,000 and US$100,000 per QALY gained (Hutton et al, 2007).

Within recent years, the immigrants are dramatically increasing in Australia, the majority come from high prevalence rate of HBV carriers in Asian countries (Korea, Vietnam, China, and Indonesia). Also, the liver cancer incidence rate is progressively rising which leads to the medical care burden a lot. Since the antiviral therapy has been developed, Robotin et al. conducted the economic evaluation for HCC prevention strategy (HCC surveillance coupled with chronic hepatitis B treatment) compared with HCC surveillance alone. The effectiveness shows that can reduce 52% cirrhosis, 47% HCC incidence, and 56% HBV-related death. Compared with current practice (without surveillance), the cost was AU$12,956 per QALY gained. Apparently, the HCC surveillance combining hepatitis B treatment can significantly reduce the healthcare burden of HCC (Robotin et al., 2009).

In 2011, Wong et al. initiated the economic evaluation to evaluate two strategies, including screen and treat, screen, treat, and vaccinate, compared with no screening. Among those aged 20-65 living in the North American immigrants, the costs of per QALY gained were US$69,209 compared with no screening and US$3,648,123 for screening + treat + vaccinate compared with screening + treat. Using the probabilistic sensitivity analysis to capture the uncertainty, given on cost of ICER <US$100,000, compared with no screening, the probabilities were 59% and 55% of being cost-effectiveness for screen+treat and screen+treat+vaccinate. It shows the moderate acceptability for the screen+treat policy (Wong et al., 2011).

In Netherland, the health care for migrants is needed for large population recently,

doi:10.6342/NTU201703133

especially for those come from countries with high prevalence rate of HBV infection. In 2010, Veldhuijzen et al. proposed economic evaluation for the screening combined subsequent treatment for eligible population versus no screening strategy, targeted on the migrants' status in Netherland using the health care perspective. Taking the medical compliance, contact tracing, sexual transmission, checkup attendance, etc. into account, the one-shot screening for HBsAg infection can reduce 10% mortality due to HBV-related. The incremental cost-effective ratio for screening combining treatment was Euro 8966 for per QALY gained compared with no screening no treatment (Veldhuijzen et al., 2010).

The HBV prevalence in Italy is low (<2%), but the newborn vaccination has been initiated from 1991. However, for the high-risk group, including immigrants, drug injection, dialysis, under high transmission rate, etc, the screening for HBV would be tend to considerate for high-risk. Assumed on the population aged 35 with 7% prevalence rate of HBV infection, the strategy with one-test screen+treat compared with no screening and no treatment shows the cost was Euro$18,255.97 per QALY gained for screen+treat compared with no screening. Based on the probabilistic sensitivity approach, the probability of 95% of being cost-effective given on the threshold Euro$40,000. The result also supports the policy of screening with subsequent antiviral therapy for those high-risk population (Ruggeri, et al., 2011).

The new-arriving adult immigrants in Canadian were increasing, however, the prevalence rate of HBV is higher than local residents. Rossi et al. also conducted the economic evaluation with societal perspective to investigate the optimal strategy compared with no screening, there were: (a)universal vaccination, (b)screening for prior immunity and vaccination, (c)HBV screening and treatment, (d)combined HBV screening and prior immunity, treatment, and vaccination. Compared with no screening,

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the result shows the cost US$40,880 per QALY gained for HBV screening combining treatment. The sensitivity analysis also demonstrates the incremental cost-effectiveness ratio is more cost-effective for immigrants aged <55 (Rossi, et al., 2013).

The drugs of antiviral therapy for HBV carriers, including oral and IFN injection, have been developed in recent two decades, but the effectiveness is different from type by type. According to those previous economic appraisal results, the strategy combining screen+treat was optimal for HBV screening. But, the efficacy of antiviral treatment of HBV would affect the results of economic analysis due to medical care for treatment failure on HBV carriers. In 2011, Eckman et al. proposed the economic evaluation for HBsAg screening combined different treatment approach based on the low prevalence rate of HBV infection (2%). Compared with no screening no treatment, the alternative strategies included HBV screening combining (a)peglated interferon-α2a for 48 weeks, (b)low-cost nucleoside agent with high rate of developing viral resistance for 48 weeks, (c)prolonged treatment with low-cost, high resistance, (d)prolonged treatment with high-cost, low-rate of developing viral resistance. About the antiviral drugs, regarding the efficacy reported by literature, the lamivudine presented low-cost and high-resistance; tenofovir showed high-cost and low-resistance, those parameters were also recruited for decision analysis. The result shows the strategy with low-cost nucleoside agent with high-resistance is cost-effective and the cost is US$29,230 per QALY gained (EcKman et al., 2011).

Targeted on special subpopulation

The cancer patients under chemotherapy is dramatically increasing due to high cancer incidence and new therapy development. However, the efficacy of chemotherapy is different from subject to subject, even the international standard therapy procedure

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(R-CHOP treatment) for lymphoma. Zurawska et al. evaluated the strategies of (a)screen-all, (b)screen for high-risk population compared with no screening. Those HBV positive patients were referral to antiviral therapy following the screening. Assumed all HBV never taking treatment and R-CHOP treatment for lymphoma after HBV antiviral therapy. The outcome was measured by death after 1-year follow-up. The screen-all strategy is dominant for lymphoma patients and the patient survival is better than no-screen or screen for high-risk (Zurawska et al., 2012).

In conclusion, based on the recent studies focused on HBV screening for adults, the strategy of HBV screening combining antiviral therapy is the dominant approach to reduce the care burden of HBV-related diseases, HCC incidence and mortality regardless high prevalence rate, high-risk group in low prevalence, or special sub group. Those evidence have been summarized in Table 2.2.

Efficacy of HBV antiviral treatment for reducing HCC, cirrhotic disease, and mortality

Chronic hepatitis B is progressing factor for liver cirrhosis and HCC. In Taiwan, the clinical result shows the significant reduction for HCC by using Lamivudine through reducing the active inflammation in liver (Liaw et al., 2004). Some treatment with Lamivudine might yield resistance to fail the treatment, other antiviral therapy developed and enhance the efficacy for HCV treatment. On the other hand, some studies also reported the treatment efficacy is highly dependent on the genotype. In 2009, Yang et al. conducted meta-analysis to evaluate the interferon therapy on the reduction of progression rates to demonstrate the significantly reducing incidence of liver cirrhosis and HCC with the efficacy of 35% and 41% (Yang et al., 2009). So far, there were a lot papers reported the efficacy based on the short follow-up time, therefore, the efficacy of

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HBV treatment in Taiwan based on multicenter with cirrhosis patients has been investigated with large database. Compared with non-treated cohort, the entecavir therapy could reduce 60% of HCC with long-term follow-up for cirrhosis and significantly reduce variceal bleeding, and other liver-related disease (Su et al., 2016). Compared with successful rate of ant-HCV therapy, the top challenge for ant-HBV therapy is the drug resistance due to the DNA mutation after the treatment, therefore, so far, there is still some new drugs developed to conquer this problem and enhance the SVR rate to eliminate HBV .

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Table 2. 2 Summary of cost-effectiveness analysis for secondary prevention by hepatitis B screening

Author	Year	Study population	Method/Model	Study design/Strategies	Outcome
Adibi et al.	2004	premarriage individuals/ Iran	Decision analysis model	① strategies 1：HBsAg screen ② strategies 2：HBsAg screen+ HBcAb screen+ preventive protocol Vs. No screening and no prevention.	Cost saving. The average cost effectiveness of strategies 1 and 2 were $202 and $197 for each chronic HBV infection prevented.
Hutton et al.	2007	Asian and Pacific Islander adults/ United States.	Decision Tree and Markov Model	①Universal Vaccination ②Screen and Treat ③Screen, Treat, and Vaccinate ④Screen, Treat, and Ring Vaccinate Vs. Status Quo(voluntary screening only)	Compared with Status Quo, a screen-and-treat strategy and a screen, treat, and ring Vaccinate strategy were cost-effective (about $36 000 to $40 000 per QALY gained).
Robotin et al.	2009	Asian-born populations aged ⩾35 years /Australia	Markov model	①HCC Surveillance ②HCC Prevention (HCC Surveillance +CHB treatment) Vs. Current practice (limited treatment of CHB and some HCC surveillance)	1.HCC prevention was a cost-effective public health strategy 2.Compared to current practice, ①HCC Surveillance ： ICER：AU$401,516/QALY gained ② HCC Prevention： ICER：AU$12,956/QALY gained
Veldhuijzen et al.	2010	Migrants/ Netherlands	Markov chain model	one-off systematic screening + treatment Vs. Status Quo(no screening)	1.cost-effective 2. Compared with not screening, ICER of screening is euros (€) 8966 per QALY gained.

doi:10.6342/NTU201703133

Author	Year	Study population	Method/Model	Study design/Strategies	Outcome
Wong et al.	2011	20-65 years old immigrants /Canada	Markov model、sensitivity analysis	1.Tenofovir for treatment： ①Screen and Treat ② Screen, Vaccinate and Treat Vs No screening 2.Entecavir for treatment： ①Screen and Treat ②Screen, Vaccinate and Treat Vs No screening	The 'Screen and Treat' is still likely to be moderately cost-effective.
Ruggeri et al.	2011	Patients at risk/Italy	Markov model of natural history of disease、sensitivity analysis	HBV screening + treatment Strategy Vs treatment Strategy	Screening plus treatment Strategy was cost-effectiveness in comparison with sole treatment Strategy.(€17179/QALY)
Rossi et al.	2013	Newly-arriving adult Canadian immigrants	Decision-analytic tree and Markov process to natural history of HBV disease	① universal vaccination, ② screening for prior immunity and vaccination, ③chronic HBV screening and treatment ④ combined screening for chronic HBV and prior immunity, treatment and vaccination vs No intervention	Chronic HBV screening and treatment was found to be the most cost-effective intervention and was estimated to cost $40,880 per additional QALY gained.
Nayagam et al.	2016	participants (aged ≥30 years)/The Gambia.	decision tree with a Markov state transition model	Screen and treat intervention vs. Current practice	The screen and treat intervention has ICERs of $540 per DALY averted, $645 per life-year saved, and $511 per QALY gained, compared with current practice.

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2.3 Secondary prevention for HCC by hepatitis C screening and treatment

The prevalence rate HCV infection is about 2.3% to 2.8% in the world, but some areas shows the endemic high prevalence rate of HCV, such as high prevalence rate in southern and eastern Taiwan (>15%). Compared with the HCV infection in the world, the HCV is the major cause for hepatitis-related disease and HCC, rather than HBV contributes in Asian countries. The transmission pathway of HCV is quite similar to HIV infection, such as inadequate blood contact/transfusion, sexual transmission, organ transplantation, drug infection, etc. Therefore, it is important task to prevent the HCV transmission broadly spread.

In 2013, Urbanus et al. proposed the cost-effectiveness analysis for antenatal National Screening Program for all women or non-western immigrants to compare with no routine screening program. The proportion of genotype of HCV infection was simulated based on the Netherland background data and the treatment depended on genotype was also simulated by recommended guideline. Compared with no routine screening for HCV, the costs were €19,505 and €17, 533 per QALY gained for all women and non-Western migrants, respectively. Given on the €20,000 as threshold, the cost for screening policy on non-Western migrants is more cost-effective than all women, but the probability is still low (Urbanus et al., 2013). Among those baby-boomer (aged 40-64) is large proportion of population in US whose HCV positive rate is about 5% and higher than general population because those are under more risk factors of HCV infection, such as blood transfusion, diabetes, multiple sexual partners. Therefore, in 2013, Liu et al. proposed the economic analysis with 9 combining strategies that combined three-type of screening (no screening, risk-based, birth-cohort one-shot) and three-type of treatments (standard therapy, IL-28B guided triple therapy, universal triple therapy). Compared with no screening, the one-shot HCV screening for

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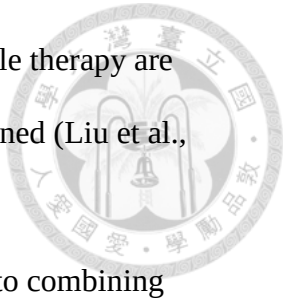

those baby-boomers and followed by IL-28B-guided or universal triple therapy are cost-effectiveness with US$68,948 and US$70,309 for per QALY gained (Liu et al., 2013).

The HCV treatment has been improved from general interferon to combining therapy and increased the sustained virological response (SVR) higher. Those SVR is quite dependent on the HCV gene-type, for example, the SVR rate of genotype-type guide are 75-80% and 85-95% for HCV-1 and HCV-2, respectively in Taiwan. Before treatment plan, the cost for the genotype examination should be paid first, otherwise, treatment all HCV patients with same plan but get the different SVR rate. Therefore, this is good scenario to conduct the economic appraisal with cost-effectiveness for decision. In 2015, Wong et al. conducted 4 strategies to evaluate the optimal strategy for HCV screening and treatment, including (a)no screening, (b)screening and treatment with pegylated interferon + ribavirin, (c) screening and treatment with pegylated interferon+ ribavirin-based direct-acting antiviral agents, (d) screening and treatment with interferon free direct-acting antiviral (DAA) agents. About the direct-acting approach, those who of having genotype 1 infection will treat simeprevir-based combination therapy, but for those who of genotype 2/3 will treat sofosbuvir-based combination therapy, and others genotypes will offer peginterferon-ribavirin. Two cohorts based on aged 25-64 and 45-64 Canadian were proposed to simulate with healthcare perspective. The result shows the incremental cost-effectiveness ratio for DAA strategy (d) was US$34783 per QALY gained among aged 25-64 and for strategy (b) was US$34,359 per QALY among aged 45-64. The results demonstrated the sensitivity analysis was high dependent on the different scenario (Wong et al., 2015).

According a lot of treatment results based on multiple countries, the hepatitis virus C virus treatment should be guided by HCV genotype to yield the high efficacy to

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eliminate the HCV successfully with more than 95% possibility. Therefore, the direct-acting antivirals (DAAs) has been proposed as guideline for clinical treatment. But, this treatment is limited due to the effective drug for treatment is very costly and the cost is varied by different combination of drug uses. Recently, Aggarwal et al. proposed the economic analysis based on India for DAAs compared with no treatment using the healthcare perspective, the results shows cost-saving with 10-year for overall and cirrhosis as well, increasing 8.02 years of life-expectancy, and increasing 3.89 QALY. The over efficacy of this DAAs treatment can expect to prevent many cases from decompensated cirrhosis, HCC, and HCV-related diseases (Aggarwal et al., 2017). In Hong Kong, Li et al. also did the economic analysis for the DAA-based treatment compared with INF-based treatment, the results show the optimal strategy of DAA by ombitasvir/partiaprevir plus dasabuvir compared with naïve treatment regardless the general or cirrhosis HCV patients based on the 70% proportion of HCV genotype 1 in Hong Kong. The DAAs treatment can be cost-effective for HCV treatment even the budget increase (Li et al., 2017).

The treatment for HCV infection has been made dramatically and significantly improvement to enhance the rate or SVR. In recent 10 years, those clinical reports also proved the effectiveness is quite highly dependent on the HCV genotype. Therefore, the DAAs (direct-acting antivirals) has been widely suggested and recommended by liver association. According to perspective of healthcare payment, the DAAs strategy can be achieved high yield of high SVR and successfully eradicates the HCV infection, then reduces the liver cirrhosis, HCC, and HCV-related diseases. Regarding some economic evaluation based on different status and background by countries, those results also supported the DAAs can be cost-effective for HCV treatment, but the variance would be dependent on the cost of drug, cirrhosis management, and expenditure of medical care.

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Those results have been demonstrated on the following Table 2.3.

Efficacy of HCV antiviral treatment for reducing HCC mortality

About the therapy for antiviral HCV, the SVR is quite high applying for HCV eradication. In 2017, Bang et al. conducted the meta-analysis combining 49 studies with long-term follow-up. The results demonstrate that HCV antiviral therapy could reduce 61% of HCC, 62% of all-cause mortality, and 64% of liver-specific mortality. Focused on the SVR was achieved, compared with no-SVR, the efficacy shows antiviral therapy could reduce 80% of HCC. This indicated that the efficacy of antiviral therapy for HCV is more promising than HBV therapy (Bang et al., 2017).

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Table 2. 3 Summary of cost-effectiveness analysis for secondary prevention by hepatitis C screening and treatment

Author	Year	Study population	Method/Model	Study design/Strategies	Outcome
Coffin et al.	2012	Population aged 20-69 years / United States	Markov Model、Decision analytic model	Risk-factor screening + one-time general population screening Vs. Risk-factor screening	1. Cost-effective 2.Compared to current guidelines, incremental cost per quality-adjusted life year gained (ICER) was $7900 for general population screening
Urbanus et al.	2013	Pregnant women and first-generation non-Western women / Netherlands	Markov model	①HCV screening all pregnant women plus treatment ②HCV screening only non-Western pregnant women plus treatment Vs. current practice (no routine HCV screening)	1. HCV screening for pregnant women is not cost-effective for women in general. 2. HCV screening for first-generation non-Western women shows a modest cost-effective outcome.
Liu et al.	2013	40–74 year-old asymptotic adults /U.S.	Markov model	① No screening+ Universal triple therapy ② No screening+ IL-28B-guided triple therapy ③Risk-based screening+ Standard therapy ④Risk-based screening+ Universal triple therapy ⑤Risk-based screening+ IL-28B-guided triple therapy ⑥Birth-cohort screening+ Standard therapy ⑦Birth-cohort screening+ Universal triple therapy ⑧ Birth-cohort screening+IL-28B-guided triple therapy	Cost-effectiveness of one-time birth-cohort HCV+(Universal triple therapy or IL-28B-guided triple therapy) screening is comparable to other screening programs

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Author	Year	Study population	Method/Model	Study design/Strategies	Outcome
				Vs. No screening+ Standard therapy	
Miners et al.	2014	Migrant populations /UK	Markov model.	Screening (Antibody test for HCV) Vs. no intervention	1.Testing UK migrants for HCV could be cost-effective. 2.ICER：£23 200 per additional QALY
Wong et al.	2015	Residents in 2 age groups: 25–64 and 45–64 years of age/Canada	State-transition model	①screen and treat with pegylated interferon plus ribavarin ② screen and treat with pegylated interferon and ribavarin–based DAAs ③ screen and treat with interferon-free DAAs. Vs. no screening	A selective one-time HCV screening program would likely be cost-effective.
Jayasekera et al.	2017	Patients with HCV genotype 1 infection / United States	Decision-analytic Markov model	2nd Gen DAAs-based treatment (interferon-free 2nd Gen DAAs) Vs. 1st Gen DAAs-based treatment (PR +1st Gen DAAs)+untreated	2nd Gen DAAs-based treatment was cost effective and cost saving as compared to 1st Gen DAAs-based treatment.
Li et al.	2017	Patients with chronic HCV genotype 1 infection /Hong Kong	Decision analytic model	DAA-based treatments vs. INF-based treatment	DAA based treatments are cost-effective alternatives to INF-based treatment.
Aggarwal et al.	2017	HCV-infected population/ India	individual-level Markov state-transition mode	DAA-based treatment vs. no treatment	HCV treatment with DAAs became cost-effective within 2 years and cost-saving within 10 years.

DAAs: Direct-acting antivirals

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2.4 Secondary prevention for HCC by screening

The liver cancer is the second leading cause of cancer incidence and mortality in Taiwan with these two decades. The major reason is the HBV infection through vertical transmission then caused the high prevalence rate of HBV carriers in Taiwan. The liver cancer screening using abdominal sonography or biomarkers have been discussed for many years ago, but the effectiveness is till controversial because the survival gain is not sufficient to invest based on the medical treatment and technique. However, new approaches have been discovered and developed in recent years, such as radiofrequency ablation (RFA), liver transplantation, liver resection, Transarterial Chemoembolization (TACE), and target therapy, which combined screening with early-detection to save life-year more than conventional approach. Therefore, the economic evaluation for the HCC screening combined different modalities (ex. AFP, sonography, MRI, etc.) and treatment to investigate the optimal strategy for fighting HCC burden.

In 1991, Chen et al. conducted the community-based screening for high-risk group of HBV carriers of 7 townships in Taiwan. The two-stage approach was applied for those who of having one or more positive results among six biomarkers (HBV, HCV, AFP, ALT, AST, family history) were referred for abdominal sonography screening then sent for clinical further diagnosis. Overall with 16,652 subjects were recruited. There were 458 patients were diagnosed as HCC using the linkage of National Cancer Registry based on 4,838 positive cases from first stage screening. After 7-year mean follow-up time, compared with non-attenders, the efficacy of HCC mortality was 24%. After adjustment for other potential factors, the efficacy was estimated by 41% (Chen et al., 2002). Besides the high-risk program by 7 townships in Taiwan, between 1992 and 1997, our government initiated Taiwan Multicentre Cancer Screening (TAMCAS)

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program based on multiple hospital to enroll those family relatives with family history to participate the screening program, which included breast cancer, colorectal cancer, and liver cancer. Among these six years, total 20,348 subjects were recruited, but 14,943 subjects completed screening at least once. The National Cancer Registry and Mortality Registry were applied for HCC diagnosis. The cumulative survival shows 65%, 48%, 40.3%, 32.8%, and 30.9% for 1-year, 2-year,3-year, 5-year, respectively. The efficacy of screening, screen-detected vs. post-screening, shows 27% HCC mortality reduction (Liao et al., 2011).

So far, there was no nationwide screening program in Taiwan for liver cancer, even the high incidence rate and mortality of liver cancer. Since 1990s, some community-based screening program was implemented using two-stage approach to improve the life-year gained for HCC. However, the abdominal sonography technique was applied to surveillance of hepatitis population. About these methods, there are still have pros and cons for comparison and discussion. Two-stage approach would be costly on the biomarkers examination, but the sonographic screening would face the difficulty on the high compliance. In 2014, Yeh et al. carried out the mass screening for all residents in Changhua using abdominal sonography for aged 45-69 based on the community-based integrated screening. After adjustment for the potential confounding factors, the efficacy significantly reached 31% mortality reduction for HCC (Yeh et al., 2014). Therefore, Kuo et al. initiated the economic analysis for both mass screening with two-stage approach and abdnominal sonographic for all compared with no screening. Given on the 60% attendance rate of two-stage approach and 80% attendance rate for abdominal sonography, the costs were US$39,825 for sonographic screening for all and US$49,733 for two-stage approach screening per QALY gained, compared with

doi:10.6342/NTU201703133

no screening. It manifests that mass screening using sonography is more cost-effective than two-stage strategy. Using the sensitivity analysis for inter-screening interval and initial age of screening, the results recommended the screening strategy of initiated age 50 with abdominal sonography is the optimal approach for mass screening (Kuo et al., 2016).

Some new biomarkers and genotypes have been reported that associated with HCC incident risk or poor prognosis. In Italian cancer prevention, some studies have been proved that semiannual surveillance can find more early-detected HCC to gain more life-year. In 2012, Cucchetti conducted the economic analysis to compare the annual with semiannual surveillance based on Italian situation for general cirrhotic population care. Given on the HCC incidence rate was 5%, the costs of semi-annual were Euro$1997 and Euro$3814 per QALM (quality-adjusted life-month) for compensated and decompensated cirrhosis respectively. This revealed the semiannual surveillance is more cost-effective compared with annual surveillance program (Cucchetti et al., 2012).

In 2017, Goossens et al., composed those factors to generate the risk for individuals combining 186-gene-based risk score, EGF genotype-based risk score, and other personal characteristics and clinical data. Simulated 10,000 patients aged over 50 with compensated liver cirrhosis were conducted to cost-effectiveness by different recommended screening strategies based on the risk-stratified for high-, intermediate-, and low-risk groups. The data shows the specificity was dependent on HCC incidence rate. The economic appraisal demonstrated the risk-stratified strategies for high- and intermediate-risk were cost-effective compared with existing policy using abdominal sonography biennial screening. About the high-tech add-on abbreviated MRI (AMRI), the low incremental cost-effectiveness ratio was showed for high- and intermediate-risk

doi:10.6342/NTU201703133

group (ICER US$2,100/per QALY) (Goossens et al., 2017).

So far, there is no evidence-based randomized controlled trial (RCT) for liver cancer screening to demonstrate the efficacy of HCC mortality reduction which was contributed by early detection to save life significantly. However, some studies which were reviewed by our literature review, it manifests that we still need the further study to investigate the screening efficacy of specific morality reduction based on the novel and advanced techniques and target therapy for HCC treatment, especially for those areas/countries of having high endemic of hepatitis. Those studies have been reported the efficacy for HCC screening were listed on Table 2.4.

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Table 2. 4 Summary of cost-effectiveness analysis for secondary prevention by HCC Screening

Author	Year	Study population	Method/Model	Study design/Strategies	Outcome
Chen et al.	2002	High-risk	Community-based	Two-stage approach	Attenders vs. non-attender: 24%(-52%, 62%) After adjustment for other potential factors: 41%(-20%, 71%)
Liao et al.	2011	High-risk	Multicentre	Hospital-based with sonography	HCC mortality reduction: 27% (1%-46%)
Cucchetti et al.	2012	Adult cirrhotic Patients/Italian	Markov model	semi-annual screening vs. annual screening	1.Semi-annual surveillance leads to a modest survival benefit in comparison with annual surveillance. 2.Both surveillance strategies for HCC in cirrhotic patients can be recommended
Yeh et al.	2014	community residents aged 45-69 years / Taiwan Changhua County	multivariable logistic regression、goodness of-fit	Mass AUS screening for HCC vs Risk Score-Guided Invitation	The study demonstrated a 31% reduction in HCC mortality by comparing those individuals invited to a community-based AUS screening with an uninvited group using a risk score-guided invitation scheme.
Kuo et al.	2016	Residents (aged ≥40 years)/ Taiwan	Markov decision model with a societal perspective and a	①Two-stage biomarker-ultrasound method ② mass screening using abdominal ultrasonography (AUS)	Mass screening using AUS is more cost effective than two-stage biomarker-ultrasound screening.

doi:10.6342/NTU201703133

Author	Year	Study population	Method/Model	Study design/Strategies	Outcome
			lifetime horizon	vs no screening	①ICER：USD49733 per life-year gain ②ICER：USD39825 per life-year gain
Goossens et al.	2017	50-year-old subjects with compensated Cirrhosis / United States	Markov decision-analytic modeling	① Risk-stratified strategies (for high–intermediate–low risk groups) ② Non-stratified experimental strategies Vs. Regular US screening	Risk-stratified HCC surveillance strategies targeting high- and intermediate-risk patients with cirrhosis are cost-effective.

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Chapter 3 Structure of CEA and evolution of intervention program for HCC

3.1 Overall framework of economic appraisal of intervention program of HCC

Figure 3.1 shows the backbone of economic appraisal for intervention program of HCC. The consideration of the overall structure of economic evaluation for population-based screening involves the invitation of screener in population registry, the disease natural history, the yield of true positive cases, false positive cases, false negative cases, true negative cases depending on test characteristics. True negative cases may be related to induce negative costs due to reassurance of true negative status, which in turn increase production. False positive cases may lead to induced positive costs because of costs involved in referral and confirmatory process. False negative cases increase treatment costs in association with advanced diseases. Prevalent/incident cases get involved with early treatment costs and probably augmented costs as suggested above. In addition to direct costs, indirect costs related to production loss in screening service or delay treatment are also taken into account.

Each cases diagnosed outside screen (interval cancer) or detected in the screen (prevalent screen or incident screen) can be dealt with in different approaches with different costs. Non-attenders often delay treatment and die early. Interval cancers may have delayed treatment. Both may have costs of terminal care. Outcome measurements for effectiveness are advanced cancer or chronic disease, subsequent complications or disability, death, and life-expectancy.

Methods of economic evaluation include cost-effectiveness/utility analysis and cost-benefit analysis. In cost-benefit analysis, effectiveness is translated into benefit in terms of human capital approach or willingness to pay (WTP). However, this thesis does

doi:10.6342/NTU201703133

not consider doing CBA analysis,

3.2 Evidence-based prevention, surveillance, and treatment and therapy of HCC

Figure 3.2 shows three levels of prevention, successive surveillance, and treatment and therapy of HCC in the light of EBM.

Prevention of HCC has evolved in parallel with the advent of new prevention, early detection, and therapeutic intervention methods, including life style modification, screening, and pharmacological therapy. Monitoring high-risk group for hepatocellular carcinoma (HCC) with scheduled interval for the check with abdominal ultrasonography designed before the era of anti-viral therapy for hepatitis B/C had better be re-contemplated. The reduction in hepatitis B virus-related infection due to the administration of hepatitis B vaccine for the middle-age adults and the emerging new etiology of HCC beyond virus-related infection like type 2 diabetes prompts health policy-makers to consider the risk profiling of surveillance policies for these new target subjects.

The introduction of mass screening for liver cancer with abdominal ultrasonography in the area with high incidence of HCC also leads to the possibility of modifying the policies of surveillance for different risk groups.

It is timely to propose surveillance policy fitting with precision medicine, namely personalized surveillance and treatment schedule due to the emerging etiology of non-virus related HCC, the administration of abdominal ultrasonography screening, the administration of new method (such as Fibroscan) for early detection of liver cirrhosis and fatty liver, and the advent of new anti-viral therapy for hepatitis B and C virus infection.

Briefly, community-based surveillance of digestive diseases had better be updated

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as a result of the advent of new intervention methods (including primary, secondary, and tertiary prevention) for various types of diseases. A series of illustrations accrued from community-based integrated screening program is delivered from universal evidence-based practice to personalized preventive strategies. The presentation will also cover how to evaluate the efficacy and cost-effectiveness of surveillance of the disease of interest while different surveillance strategies are considered.

3.3 Universal HBV vaccination program

The HBV infection is the major cause for HCC incidence which is the first/second leading cause of cancer incidence in Taiwan. Not only the HBV leads to the impact of HCC, but also plays the important role for the burden of chronic liver disease, like liver cirrhosis. The transmission pathway includes vertical and horizontal types, but the vertical pathway from mother-to-infant is the dominant way in Taiwan. Taking the advantage of DNA-type of hepatitis B virus, the vaccination to combat HBV infection was successfully developed and applied to stop the vertical transmission in Taiwan using the universal vaccination program. Combining HBV vaccination and hepatitis B immune globulin is the successful key point for this battle of HBV elimination. First stage in 1984-1985, those who were pregnant women were surveyed by HBsAg and HBeAg and the hepatitis B immune globulin was implemented for those highly infectious mother whose HBeAg positive and carriers during the newborn delivery. After the preparation for the administration and resource arrangement, the universal vaccination program was initiated since 1986 as second stage. The coverage rate of HBV vaccination was more than 90%.

Besides the onward program, the catch-up vaccination program was implemented between 1987 and 1989 for those preschool children. During 1988 to 1993, some

doi:10.6342/NTU201703133

catch-up vaccination also reached to children and young adults among aged 5-39 who were susceptible to HBV infection (Chen et al., 1987). The effectiveness of HBV vaccination was varied by the prevalence of HBV infection. For example, the vaccination can reduce 91% of hepatitis B infection before aged less than 25 and decrease the HCC about 80% for aged 5-29, and more than 90% reduction on HCC mortality, but this could not apply to the low endemic country (Locarnini et al., 2015). On the hand, the HBV vaccination could not be assured 100% protection for the newborn baby because some babies are failure to response with vaccination immunization and some children/adults might be attrited by time to lose the protection. In 2007, Ni et al. used the serum sample in 2004 from Taipei county which recruited 18,779 subjects aged between 20 and 30 and born after universal vaccination program initiation. The HBsAg prevalence rate were demonstrated by year of birth, besides the birth cohorts of 2003-2004 and 1986-1989, those vaccination coverage rate was more than 90%. The prevalence rate among those aged 1-14 were lower than 1%, but those who aged >10 shows the prevalence rate were more than 10% and increased by age. This study also revealed those immunization failures caused by maternal HBV infection with active status (Ni et al., 2007). In 2012, Su et al. conducted the survey for those young adults aged 15-24 for incidence of acute hepatitis B in Taiwan, the results show the increasing infection rate is associated with age increased, from 0.78 to 2.33 per 100,000 (Su et al., 2012). Therefore, there is still small portion of population with HBV carriers or those who are susceptible to HBV infection. The chorological schedule for HBV vaccination in Taiwan has been illustrated on Figure 3.3.

3.4 Screening program for HCC

According to the survey report by many studies varied by counties, the

doi:10.6342/NTU201703133

prevalence rate among adults is about 15-20% and estimates more than 200 million population who are chronic hepatitis B virus infection as carriers, which are not protected by universal vaccination program. For those who are HBV infection and carriers, there are some screening approaches were recommended by experience form clinical and epidemiological studies. In 1991, Chen et al. conducted 7 townships in Taiwan which recruited 16,652 subjects using two-stage screening approach to find early HHC to reduce the mortality. For the first stage, there were 6 markers were recruited for serum examination and those who were one of marker as positive, including HBV(+), or HCV(+), AFP>=20ng/mL, AST>=40, ALT>=45, and family history. For the second stage, the abdominal sonography was applied for the those who of having >=1 markers as positive. The regular surveillance was suggested by 6-month for cirrhosis and 1-year for chronic liver disease. After mean follow-up time with 7 years, compared with non-attenders, this study shows 24% mortality reduction for those who attended the two-stage screening, but the efficacy of mortality reduction was 41% after adjustment for other factors (Chen et al., 2002). Besides the 7 townships with high-risk population, this two-stage approach also was applied to general population, including Keelung (Chen et al., 2004) and Changhua (Yeh et al., 2010) which was based on the community integrated screening platform. In 2006, Lu et al. conducted the community-based integrated screening data in Tainan, they found the platelet could make contribution on the liver cirrhosis and HCC prediction as surrogate endpoint for screening. Therefore, the platelet was applied to add prediction model for Changhua community.

Besides the two-stage community-based screening, in 1992, our government initiated the cancer screening for high-risk group, including colorectal cancer, breast cancer, and liver cancer using the Multicenter Cancer Screening (TAMCAS) based on

doi:10.6342/NTU201703133

hospital-based. Recruiting 20, 348 subjects with HCC high-risk, the efficacy shows 27% mortality reduction after adjustment for potential risk factors with over 15 years follow-up (Liao et al., 2011).

In 2008, regarding the factors for HCC in Taiwan, the previous have reported that diabetes and metabolic factors might play the important roles for HCC incidence, especially for those who were not infected by hepatitis viruses (Lai et al, 2008). Therefore, the Health Bureau of Changhua County implemented the population-wide liver screening using abdominal sonography based on risk stratification approach. The risk score was generated from original 6 biomarkers combing platelet, diabetes to predict the individual risk score (Yeh et al., 2010).

In 2010, the HBV DNA was found that the titer can be represented the active of hepatitis virus in liver for those who of having HBV carriers. In 2011, Yang et al. conducted the community-based Taiwanese REVEAL-HBV study to predict the risk of HCC incidence and also collected the cohort from Hong Kong and Korea to produce the validation cohort for predicted model. The AUROC for the prediction perform shows the 81% at 3 years, 79.6% for 5-year, and 76.9% for 10 years. This study revealed the HBV DNA would be the good predictor for HCC incidence (Yang et al., 2011). Please see the Figure 3.4.

3.5 Anti-viral therapy for hepatitis B and C

The antiviral treatment for hepatitis B and C was developed for those who of having carriers but under the risk of liver cirrhosis and HCC incidence. In 1992, the interferon has been approved for hepatitis B carriers' treatment. According to the mechanism of interferon, there are some complication/adverse effect caused by this treatment. On the other hand, the treatment using injection would reduce the compliance of treatment. Therefore, in 1998, the oral drug-Lamivudine for anti-HBV therapy has

doi:10.6342/NTU201703133

been approved and applied to patients' care. From the clinical follow-up, the successful treatment rate of anti-HBV treatment seemed not perfect as expectation. In 2005, the new interferon- pegylated interferon-α has been discovered for wide use to reduce the complication caused by interferon. So far, besides the interferon therapy, the oral drugs for anti-HBV included Lamivudine(LAM), telbivudine (LdT), entecavir(ETV), adefovir dipivoxil (ADV), and tenofovir disoproxil fumarate (TDF). According to the treatment guideline, those drugs have been classified into first- and second-line drug to tackle the drug resistance during treatment. In 2008, the combination therapy has been proposed to combat the HBV chronic hepatitis carriers. In 2016, Su with Taiwanese C-TEAM (Cirrhosis-Taiwanese EntecAvir Multicenter) to evaluate the efficacy for the anti-viral therapy in Taiwan with long-term follow-up, the efficacy shows 60% reduction of being HCC incidence among those with liver cirrhosis (Su et al., 2016).

The interferon has been approved for anti-HCV treatment in 1989 and combining therapy with Ribavirin for HCV therapy in 1998. The new interferon-pegylated interferon-α also was applied to anti-HCV combination therapy, the efficacy was reached 70-80% successful rate. In 2014, the novel new drug-sofosbuvir (SOF) has been developed which combined with interferon and Ribavirin can reach the sustained virological response (SVR) rate more than 90%, especially for HCV genotype 1 with DAAs (Hézode et al., 2016). This result indicates that the anti-viral therapy would be promising to eradicate HCV. The more discover on anti-HCV treatment, the more improvement on the strategy of treatment, especially for the direct-acting antivirals (DAAs) development for the anti-HCV treatment. In 2017, Li et al. focused on the new oral drug for HCV treatment bases on a hundred of clinical trials to summarize the advantages for this new era: (i) interferon was replaced by interferon-free; (ii) genotype-specific drugs for all HCV genotypes; (iii) therapies combining multiple pills

doi:10.6342/NTU201703133

and a single pill per day; (iv) drug potency increased levels of SVR; (v) shortened treatment duration from 48 to 12 or 8 weeks; and (vi) therapies with oral drug regardless of prior treatment history and cirrhotic status (Li et al., 2017). About the chorological history of anti-HBV and ant-HCV therapy were demonstrated in Figure 3.5.

3.6 Alternative treatment for small HCC in the era of early detection

Radiofrequency Ablation (RFA) is a newly developed nonsurgical treatment for hepatocellular carcinoma (HCC). RFA has been demonstrated as an effective treatment modality for HCC. RFA is also a favourable method due to more infrequent serious complications and less discomfort. Besides, the technological complexity of RFA is lower than surgery. Therefore, it is anticipated to increase the efficiency of treating small HCC, especially in the country with a shortage of gastrointestinal surgeon. However, the clearance rate of tumor treated by RFA in the first hospitalization after the diagnosis is lower than surgery, so the further recurrent and the consequent hospitalization together with the associated cost may be incurred more than surgery. Therefore, the comparison between RFA and surgery on the utilization and cost of hospitalization is of paramount importance. In this thesis, we also compare the inpatient cost in the first hospitalization for small HCC treated by RFA or surgery.

3.7 Personalized surveillance for patients with SVR in the era of the anti-viral therapy

Whether to lengthen the surveillance interval for abdominal ultrasonography, especially for those showing sustained virological response (SVR) to interferon and identified as having low risk of developing hepatocellular carcinoma (HCC), with less cost but without compromising life-years gained is of great interests in the era of anti-viral therapy. In this thesis, we also assessed the economic appraisal of a multiple screening together with primary prevention of chronic diseases as opposed to single

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disease screening, and the trade-off between cost and effectiveness for risk stratification-based surveillance strategies by using a formal cost-effectiveness analysis.

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Chapter 4 Materials and Methods

4.1 Data sources

4.1.1 Time trend of epidemiological profiles of HCC

The cancer incidence cases were retrieved from National Taiwanese Cancer Registry System which is governed and supported by Health Promotion Administration, Ministry of Health and Welfare. The HCC incidence cases were defined as primary cancer between 1979 and 2013. The HCC-specific death cases between 1979 and 2013 were collected from National Taiwanese Mortality Registry System which is supported by Ministry of Interior, Taiwan and the specific causes of death were also verified by Health Promotion Administration, Ministry of Health and Welfare. About the nationwide population by year was also retrieved from National Population-based Household Registry System which is also governed by Ministry of Interior, Taiwan. All vital statistical data were reclassified by 5 ages rank for further calculation and relative risk estimation.

4.1.2 Data analysis on epidemiological profiles and effectiveness

According to the chronological events of universal HBV vaccination (1984), screening (2004), nationwide health insurance (1995), and hepatitis therapy (2004) in Taiwan and the etiological characteristics for HCC, we classified the age into 0-29, 30-49, 50-69, and 70-84 and highlighted the specific time points for reference. The crude HCC incidence, mortality, and fatality rates were calculated by gender from 1979 to 2013. Based on the available data between 1979 and 2013, the incidence arte could be distinguished for birth cohort between 1897 and 2011, therefore, the HCC incidence of age- and birth cohort were generated by gender.

The age-standardized incidence and mortality rates were adjusted by the standard

doi:10.6342/NTU201703133

population in 2000, WHO. We conducted the Poisson regression approach to estimate the risk ratios of age, gender, and period for HCC incidence and mortality as well.

4.2 Cost-effectiveness analysis for the prevention of HCC

In this thesis, we conducted the cost-effectiveness analysis for

(1) the primary and secondary prevention for HCC with single or multiple modalities

Taking no intervention of the reference group

Single modality

Universal vaccination

Anti-viral therapy for HBV

Anti-viral therapy for HCV

Anti-viral therapy for HBV and HCV

Abdominal ultrasonography biennial mass screening

Multiple modality

Universal vaccination + Anti-viral therapy for HBV and HCV

Universal vaccination + Abdominal ultrasonography biennial mass screening

Universal vaccination + Anti-viral therapy for HBV and HCV+ Abdominal ultrasonography biennial mass screening

Taking vaccination of the reference group

Universal vaccination + Anti-viral therapy for HBV and HCV

Universal vaccination + Abdominal ultrasonography biennial mass screening

Universal vaccination + Anti-viral therapy for HBV and HCV+ Abdominal ultrasonography biennial mass screening

(2) the selection of treatment with either hepatic surgery or RFA among small HCC patients, of whom the proportion grows in the era of early detection

(3) personalized surveillance for patients with successful viral response for patients

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undertaking interferon.

We applied a series of Markov decision models for different strategies in the following section.

4.2.1 Population-based Markov decision tree

Disease natural history

Figure 4.1 depicts the Markov decision tree for the disease natural history model under no intervention. The disease natural history involved a series of states, including latent, susceptible, immunity, acute hepatitis B infection, hepatitis B carrier, chronic hepatitis B (CHB), compensated and decompensated liver cirrhosis, HCC, death from HCC, death from other cause of death.

Vaccination

The decision tree related to universal vaccination was depicted in Figure 4.2. In this decision, we considered vaccination for all new born babies whose mothers complied to vaccination. In addition, pregnant mother with HBeAg positive were provided with lamivudine and HBIG. The vaccination takes effect on the prevention of horizontal transmission, and the lamivudine and HBIG prevents the vertical transmission.

Screening

The Markov decision tree for abdominal ultrasonography mass screening is depicted in Figure 4.3 We followed the framework of Figure 3.1 to follow the sequent events after screening, including true positive, false positive, screen-detected, clinically detected, and the stage-shifting accompanied with early detection.

Anti-viral therapy

The Markov chain for anti-viral therapy is the same as that of vaccination, but the effect takes place in the transition probability of the occurrence of liver cirrhosis and

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HCC.

Alternative treatment for small HCC in the era of early detection

The Markov decision tree for the alternative treatment for small HCC is depicted in Figure 4.4. In this analysis, the disease course of remission and relapse could occurred repeatedly, followed by the possible absorbing states of HCC death and competing death.

Personalized surveillance for patients with SVR in the era of the anti-viral therapy

The "risk stratification-based surveillance stratification (RSBSS)" was compared to "usual care (UC)" (Figure 4.5). For UC, patients underwent 6-monthly AUS. For RSBSS, we firstly categorized patients into low (L)-, intermediate (IM)-, and high (H)-risk group according to the well-established predictive model for HCC development with chronic hepatitis C after SVR in a medical center. Four RSBSS strategies with different surveillance interval for AUS by risk group were considered:

RSBSS-1: (H) 6-monthly; (IM) 1-yearly; (L) 2-yearly

RSBSS-2: (H) 3-monthly; (IM) 1-yearly; (L) 2-yearly

RSBSS-3: (H) 6-monthly; (IM) 6-monthly; (L) 2-yearly

RSBSS-4: (H) 3-monthly; (IM) 6-monthly; (L) 2-yearly

RSBSS-5: (H) 3-monthly; (IM) 3-monthly; (L) 1-yearly

4.2.2 Input parameters

Parameters related to disease progression, mortality rate, compliance and efficacy of primary and secondary prevention programs were derived from cancer registry in Taiwan and literatures (Table 4.1). Parameters of direct and indirect cost were based on payment from the National Health Insurance Administration in Taiwan, Ministry of Health and Welfare, empirical data from hospitals and communities (Table 4.2).

doi:10.6342/NTU201703133

4.2.3 Cost-effectiveness analysis

The incremental cost-effectiveness ration (ICER) between different approaches was used to assess the extent of cost-effectiveness. A 3% discount rate was assumed in the current cost-effectiveness analyses. We simulated a hypothetic cohort of 300,000 in the cost-effectiveness analysis for primary and second prevention for 75 years from societal perspectives. For the selection of the treatment modality of small HCC, the simulation time horizon was 5 years. For personalized surveillance, the time horizon was 8 years.

4.2.4 Probabilistic CEA

The probabilistic approach considering the joint uncertainty of parameters was adopted for the case of tertiary prevention by using Monte Carlo Markov Chain simulated 100 times. By assigning a series of specific distributions to each parameter, a probabilistic cost-effective analysis using Monte Carlo simulation was conducted.

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Chapter 5 Results

5.1 Age-specific incidence, case-fatality, and mortality with time

5.1.1. The incidence rate of HCC by different age group

According to the National Taiwan Cancer Registry Statistics, the long-term scale of HCC incidence shows the crude incidence is continuously increasing, but the age-standardized incidence rate shows the increasing rate from 1979 to 2004 and the decreasing trend from 2004 to 2013. Among those 0-29 years-old who have been protected by HBV vaccination, the incidence rate of HCC shows the light increasing from 1979 to 1994, but the decline incidence rate was demonstrated since 1995 so far, especially the dramatic decrease from 2004 forward. After the nationwide health insurance was initiated, the HCC incidence was increased but dramatically decreased onward, see Figure 5.1 (A). The decreasing trend was from 1.24 to 0.638 for overall, from 1.80 to 1.02 for male, and from 0.71 to 0.28 for female per 100,000 based on the aged under 30. This can be explained by efficacy of HBV vaccination.

For those who aged 30-49, those who were not protected by vaccination, but partial probably cured by hepatitis B therapy, the increasing incidence rate of HCC between 1995 and 2004, the incidence rate from 14.63 increased to 23.5 for overall, from 25.07 increased to 40.16 for male, and from 5.22 increased to 6.47 for female, respectively. However, the significant decreasing rate was demonstrated from 2004 to 2013, the HCC incidence rate decreased from 23.5 to 15.56 for overall, from 40.16 to 28.95 for male, and from 6.47 to 4.31 for female per 100,000 among the aged 30-49, see Figure 5.1 (B).

The similar pattern trend of HCC incidence on aged 30-49 was noted on aged 50-69 with higher incidence. The steady increasing incidence rate of HCC from 1979 to 1995, but had plateau between 1999 and 2004. The slight increasing rates of HCC

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between 1995 and 2004, from 91.55 increased to 129.82 for overall, from 131.19 increased to 190.67 for male, and from 48.30 increased to 70.79 for female, respectively. However, the significant decreasing rate was demonstrated from 2004 to 2013, the HCC incidence rates decreased to 101.91, 153.88, and 52.08 per 100,000 for overall, male, and female among the aged 50-69, respectively, see Figure 5.1 (C).

But for those who aged 70-84, the steady increasing trend from beginning to the 2013, especially from 1995 to 2004. These incidence rates were dramatically increased from 123.76 to 245.38 for overall, from 159.58 to 294.17 for male, and from 82.37 to 190.85 for female per 100,000, respectively, see Figure 5.1 (D).

Using the Poisson regression model, taking age, gender, and period into account for analysis, the results were reported in Table 5.1. Among those population aged 0-29, compared with aged 25-29, the relative risks (RR) were 0.25(95%CI: 0.22, 0.28), 0.12(95%CI: 0.10, 0.14), 0.15(95%CI: 0.13, 0.18), 0.20(95%CI: 0.18, 0.23), and 0.41(95%CI: 0.37, 0.44) for aged 0-4, 5-9, 10-14, 15-19, and 20-24, respectively, after adjustment for gender and period. They show the gradient reduction by age, the younger the more benefit, see Table 5.1. For those who aged 30-49, the incidence decreased by age and the younger the more benefit, but the effectiveness is slight less than aged 0-29. Compared with aged 45-49, the RRs were 0.17 (95%CI: 0.16, 0.18), 0.34 (95%CI: 0.33, 0.35), and 0.59 (95%CI: 0.59, 0.60) for aged 30-34, 35-39, and 40-44, respectively. However, among the aged 30-49, the risk was dramatically higher than other age group, the RR was 6.29 (95%CI: 6.10, 6.48) of male compared with female. For those aged 50-69, the incidence was demonstrated decline trend with inverse age, but benefit is less than aged 0-29 and 30-49 as well. Compared with aged 65-69, the RRs are 0.38 (95%CI: 0.38, 0.29), 0.59 (95%CI: 0.58, 0.60), and 0.80 (95%CI: 0.79, 0.81) for aged 50-54, 55-59, and 60-64, respectively. For the elders aged more than 70, the incidence of HCC

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is slightly increased by age and also was noted increased by period, see Table 5.1.

5.1.2 The mortality rate of HCC by different age group

For the mortality of HCC, the age-standardized using WHO 2000 population, the mortality rate was increased from 1979 to 2004, but the decreasing mortality was noted after 2004 among all ages. Among the population aged 0-29, the steady and significant decline trend of HCC mortality was manifested from 1984 to 2013. The mortality rates were 1.23, 0.96, 0.67, and 0.23 per 100,000 for overall aged 0-29. The similar trends also noted on male and female as well, see Figure 5.2(A).

For the aged 30-49 population, the morality rate between 1979 and 2004 was plateau, not change a lot, but the morality rate was decreased from 2004 to 2013. The mortality rates of HCC were 13.79 and 9.14 for 2004 and 2013 respectively for overall and the more decreasing rate was noted among male, from 24.31 to 16.10 from 2004 to 2013, see Figure 5.2(B).

About the HCC mortality rates on aged 50-69, the significant and steady decline trends were revealed from 1995 to 2013 for both gender. For overall aged 50-69, the morality rates were decreased from 85.93, 80.92, and 61.56 for 1995, 2004, and 2013. The phenomena were also demonstrated on male and female, see Figure 5.2(C). The mortality among aged 70 or elder demonstrated the slight increasing from 1995 to 2014, there was no decline trends. The mortality rates of HCC were 166.86, 195.65, and 208.46 for the time points of 1995, 2004, and 2013, respectively for over overall aged 70-84. The Similar trend were also revealed on male and female, see Figure 5.2 (D).

The relationship between incidence and mortality is attributed by treatment and medical technique on care and the treatment development would be highly associated with period in chronological time. Therefore, to investigate the relative risks for age, gender, and period on the HCC mortality, the poison regression was carried out for

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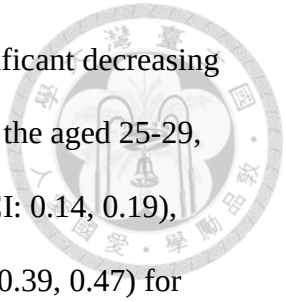

further analysis. For those who young population aged 0-29, the significant decreasing rate of HCC mortality was noted with age decreased. Compared with the aged 25-29, the RRs for HCC morality were 0.15(95%CI: 0.13, 0.18), 0.16(95%CI: 0.14, 0.19), 0.20(95%CI: 0.17, 0.22), 0.25(95%CI: 0.22, 0.28), and 0.43(95%CI: 0.39, 0.47) for aged 0-4, 4-9, 10-14, 15-19, and 20-24 respectively. The trend of HCC mortality is quite similar to the incidence in the same age group. Among those young adults aged 30-49, the significant decline trend, but the benefit is less than aged 0-29. Compared with aged 45-49, the RRs of HCC mortality were 0.16 (95%CI: 0.16, 0.17), 0.34 (95%CI: 0.33, 0.35), and 0.58 (95%CI: 0.57, 0.60) for those aged 30-34, 35-39, and 40-44, respectively. The phenomena of HCC morality in aged 30-49 is quite similar the HCC incidence, especially for age and gender. But for the period, the result shows the decline mortality of HCC associated with chronological onward. For the HCC mortality in population aged 50-69, the pattern is quite similar to the incidence. Compared with aged 65-69, the RRs were 0.35 (95%CI: 0.34, 0.35), 0.53 (95%CI: 0.52, 0.54), and 0.76 (95%CI: 0.74, 0.77) for those aged 50-54, 55-59, 60-64, respectively. For those elders, the results show the decreased HCC mortality, this phenomenon is opposite to the incidence of HCC in this age group. Compared with aged 80+, the RRs of HCC morality were 0.80 (95%CI: 0.78, 0.81) and 0.93 (95%CI: 0.91, 0.95) for aged 70-74 and 75-79, respectively. Those results have been demonstrated in Table 5.1.

5.2 Efficacy and effectiveness of primary and secondary intervention

5.2.1 Single modality

Table 5.2 shows the simulated results of a series of outcomes, including active B viral replication, hepatitis B carrier, chronic hepatitis B, compensated liver cirrhosis, decompensated liver cirrhosis, cases and deaths of HCC, and death from all causes, under different scenarios with varying single modality program for the prevention of

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HCC targeting at the Taiwanese birth cohort of 1984 with a hypothetical cohort size of 300,000. Without any intervention program, there were 266,380 acute infection, 3,998 chronic hepatitis B, 36,429 compensated liver cirrhosis, 16,372 decompensated liver cirrhosis, 16,085 HCC patients (13,523 [84%] were stage 2+), 14,336 HCC deaths, and 136,401 deaths of all causes. The universal vaccination resulted in 88% reduction of hepatitis B virus related event, including 233,462 acute infection and 3,506 chronic hepatitis B patients reduced, which led to avoidance of 14,381 decompensated liver cirrhosis, and 14,101 HCC patients. Taken together, the universal vaccination would lead to 15% (RR=0.8484, 95% CI: 0.8004, 0.8895) mortality reduction of all causes.

With the single prevention modality with anti-viral therapy, the anti-HBV drug was associated with 16% (RR=0.8430, 95% CI: 0.7466, 0.9215) of HCC death reduction compared to no intervention, and a 0.7% effectiveness on all-cause mortality death (RR=0.9926, 95% CI: 0.9840, 1.0002). The corresponding figure for anti-HCV drug was about 2% (RR=0.9790, 95% CI: 0.9536, 0.9984) and 0.09% (RR=0.9991, 95% CI: 0.9926, 1.0044). The contribution of administration of anti-viral therapy to both viruses contributed to 18% (RR=0.8228, 95% CI: 0.7275, 0.9044) mortality reduction from HCC, and 1% of all-cause of death (RR=0.9915, 95% CI: 0.9820, 0.9996).

If this cohort had only biennial mass screening with abdominal ultrasonography conducted as a prevention strategy for HCC targeting at subjects aged 50-69 years old, the HCC death would be reduced by 14% (RR=0.8615, 95% CI: 0.7984, 0.9433) compared to no intervention, and yielded 1% risk of all cause of death (RR=0.9893, 95% CI: 0.9807, 0.9977). Note that it is only screening that would change the distribution of stage of HCC. Without screening, the proportion of stage 2+ HCC was roughly 84% among all HCC patients, but the figure reduced to 54% when mass screening was applied, although the total number of HCC cases could not be changed.

doi:10.6342/NTU201703133

Nonetheless, the reduction of the absolute number of HCC cases from anti-viral therapy still decrease number of stage 2+ HCC. The effectiveness of stage 2+ HCC, either through decreased total HCC cases from anti-viral therapy or stage shifting from mass screening, was 88% (RR=0.1231, 95% CI: 0.1072, 0.1444), 15% (RR=0.8464, 95% CI: 0.7493, 0.9250), 2% (RR=0.9807, 95% CI: 0.9538, 1.0027), 17% (RR=0.8289, 95% CI: 0.7300, 0.9105), and 32% (RR=0.6767, 95% CI: 0.6333, 0.8190) from single modality of vaccination, anti-viral therapy for HBV, HCV and both HBV and HCV, and mass screening, respectively.

5.2.2 Multiple modalities

Table 5.3 shows the simulated results of different combined modality for the prevention of HCC compared to either no intervention or universal vaccination only. Taking no intervention as the reference group, it is shown that combined use of universal vaccination and anti-viral therapy was associated with 90% less HCC cases (RR=0.1018, 95% CI: 0.0826, 0.1249) and 15% less deaths (RR=0.8472, 95% CI: 0.7980, 0.8893). The corresponding figures with combined strategy of universal vaccination and mass screening were 89% (RR=0.1068, 95% CI: 0.0891, 0.1313) and 15% (RR=0.8474, 95% CI: 0.7997, 0.8884) for HCC cases and deaths, respectively. If all the three strategies were applied, the effectiveness in terms of HCC cases and deaths reduction was 91% (RR=0.0878, 95% CI: 0.0511, 0.1435) and 15% (RR=0.8469, 95% CI: 0.7935, 0.8890), respectively.

Taking vaccination only as the reference group, the effectiveness of preventing HCC cases and deaths of combined strategy of vaccination and antiviral therapy reduced to 17% (RR=0.8254, 95% CI: 0.7197, 0.9349) and 0.1% (RR=0.9986, 95% CI: 0.9925, 1.0042), respectively. The corresponding figures of combined strategy of vaccination and mass screening were 13% (RR=0.8661, 95% CI: 0.7677, 0.9671) and

doi:10.6342/NTU201703133

0.1% (RR=0.9988, 95% CI: 0.9930, 1.0051), respectively. If all the three strategies were applied, the effectiveness in terms of HCC cases and deaths reduction was 29% (RR=0.7124, 95% CI: 0.4095, 1.1455) and 0.24% (RR=0.9976, 95% CI: 9,9834, 1.0092), respectively.

5.3 Results of cost-effectiveness

5.3.1 Single and multiple modality of primary and secondary prevention

Table 5.4 shows the results of cost-effectiveness analysis of different single prevention modality for HCC. Without any intervention program, the average cost was $25,108 per person. The life-year was 65.91 years. With vaccination, the average cost per person was $3,091 and the life-year was prolonged to 67.85. Cost saving from universal vaccination program was $22,017 (ICER: -$11,334, 95% CI: -$18,110, -5,704). The results were very robust even with consideration of the uncertainty of parameters, which can be seen that all simulated points located in the fourth quadrant of the scatter incremental cost effectiveness plot (Figure 5.5 (A)), and 100% possibility of being cost-effective in the acceptability curve (AC) (Figure 5.6 (A)). This suggests that the universal vaccination program dominated unvaccinated scenario definitely because the universal vaccination program not only prolonged life but also saved cost. The same phenomenon is also observed in the combined strategies of preventing program once vaccination was considered as an option (Table 5.5). The ICERs for combined use of universal vaccination with anti-viral therapy, mass screening, and anti-viral therapy plus mass screening were -$11,239 (95% CI: -$18,000, -$5,710), -$11,219 (95% CI: -$17,776, -$5,723), and -$11,149 (95% CI: -$18,262, -$5,571), respectively. The scatter incremental cost effectiveness plot and acceptability curve are shown in Figures 5.7 and 5.8.

The other single modalities, anti-viral therapy for HBV, for HCV and for both

doi:10.6342/NTU201703133

HBV and HCV and mass screening had positive ICERs (more cost and more effectiveness). The ICERs for anti-viral therapy for HBV, for HCV and for both HBV and HCV and mass screening were $6,017 (95% CI: -$6,561, $32,815), $527 (95% CI: -$16,480, $58,799), $5,137 (95% CI: $672, $22,245), and $3,323 (95% CI: -$1,339, $16,002). The scatter incremental cost effectiveness plot and acceptability curve are shown in Figures 5.5 and 5.6 (B)-(E).

Compared with universal vaccination only, the ICERs for combined use of universal vaccination with anti-viral therapy, mass screening, and anti-viral therapy plus mass screening were $4,633 (95% CI: -$33,414, $34,875), $11,668 (95% CI: -$58,164, $31,715), and $9,102 (95% CI: -$103,320, $33,628), respectively. The scatter incremental cost effectiveness plot and acceptability curve are shown in Figures 5.9 and 5.10. The probability of being cost-effective of these combined programs given universal vaccination reached plateau to 60%-70%.

Figure 5.11-5.13 shows the summary of acceptability curve of sing and multiple modalities compared to no intervention, and the multiple program versus only vaccination.

5.3.3 Alternative treatment for small HCC in the era of early detection

Table 5.6 shows the base-case of the cost-effectiveness analysis between RFA and surgery for small HCC. The base-case shows surgery cost less ($1155.37) but earned 0.6231 life-years, which suggests surgery dominated RFA. The scattered incremental cost-effectiveness plot is shown in Figure 5.14.

5.3.4 Personalized surveillance for patients with SVR in the era of the anti-viral therapy

Table 5.7 shows the cost-effectiveness analysis for personalized surveillance for patient with chronic hepatitis C showing SVR to interferon. The life-year gained (LYG)

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increased with intensive strategies. It is very interesting to note that RSBSS-5 which extended the surveillance interval to 1 year for the low-risk group (75% in the target population) and shorten it to 3 months for the high-risk group (5% in the target population) had the same LYG as UC, but results of incurred less cost. For other RSBSSs, the cost was less than that of UC accompanied with life-years lost by 0.7 to 3 days per patient. Compared to usual care, all the simulations found RSBSSs incurred less cost (Figure 5.15). The acceptability curve between RSBSSs and UC shows that a ceiling ratio of $15,000 per life-year gained was the most cost-effective strategies for the surveillance with AUS for HCC (Figure 5.16).

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Chapter 6 Discussion

6.1 Major contributions

The contributions made from this thesis are several-fold.

(1) It provides empirical evidence from Taiwanese experience on the effectiveness of universal vaccination, two-stage and mass screening with abdominal ultrasonography, anti-viral therapy, and adequate clinical control of HCC by using time trend of age-specific epidemiology profiles of corresponding to birth cohorts eligible for various kinds of intervention programs. This is the first study to demonstrate the evidence-based information on a series of intervention programs from primary prevention to tertiary prevention.

(2) It provides a systematic economic evaluation of various combination of intervention program in terms of vaccination, screening, anti-viral therapy, surveillance after SVR, and different types of surgery by suing Taiwanese scenario of hepatitis B/C virus infection and incidence of HCC. Such a panorama of economic evaluation has been never addressed before. Doing so enables one to get a better understanding of additional costs and benefits resulting from different combinations of intervention program with each other.

6.2 Time trends of HCC epidemiology

It is very interesting to note that the overall incidence and mortality of HCC has started to decline since around 2000. Time trends in case-fatality has consistently declined since 1985 and had a dramatic decrease after 2000, five years after the introduction of national health insurance (NHI). By classifying age band into four categories, < 30 year, 30-49 years, 50-69 years, and 70+ years in accordance with the implementation of various available intervention methods for eligible birth cohorts, we

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found all the time trends of incidence of HCC except old age group (70+ years) have shown a declining trend due to each category of birth cohort experiencing each corresponding intervention program.

Regarding the HCC incidence rate in aged 30-49 and 50-69, the trend show a decline even those who were not protected by universal vaccination, especially for those aged 30-34 and 35-39. Three reasons would contribute to this result, (1) anti-viral therapy (2) vaccination reduces horizontal transmission rate, and (3) catch-up vaccination program in Taiwan for partial preschool students who were born before 1984. First, the summary report from Lin and Kao said the anti-HBV therapy could gain high reduction efficacy of HCC incidence from chronic hepatitis patients or liver cirrhosis, i.e. efficacies were 63%, 60%, 63%, and 45% of Taiwanese nationwide study, Taiwanese C-Team, Japan cohort, .and Hong Kong hospital-based cohort, respectively. Second, Lin et al. reported in 2003 that the prevalence rate of HBV by vaccinated and unvaccinated subjects in Hualien, eastern county with high endemic HBV, besides the reduction of HBsAg positive rate after vaccination, the HBV carrier rate also reduced for those who were not covered by vaccination. These results indicated that HBV vaccination might protect those who do not protect by vaccination through reducing the horizontal transmission rate, also explicated as herd immunity (Lin et al., 2003). Third, with the chronological time frame of HBV vaccination in Taiwan, there were three cohorts were carried out for catch-up vaccination program for birth 1972-1978 as junior and senior high schools, 1977-1984 as elementary schools, and 1982-1986 as preschool, partially.

Based on the scenario of HBV/HCV natural history, those majority of HCC mortality would be attributed by HCC incidence due to the poor prognosis. Therefore, our results show the similar trends between HCC incidence and mortality even the

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fatality rate of HCC has been made great improvement since the nationwide health insurance initiated. The fatality rates were significantly reduced according to the 1994 of nationwide health insurance and 2004 of anti-viral therapy applied for clinical care.

6.3 Effectiveness of intervention

According to the Locarnini et al. reported the review for the HBV control policy and effectiveness, the efficacy of HBV vaccination for newborn would reach 91% of prevalence rate of HBsAg carriers for population aged <25 and decreased the 80% of HCC incidence for aged 25-29 (Locarnini et al., 2015). Compared with the finding in our study based on the birth cohort after universal vaccination program initiation, after adjustment for the gender and period effect, the efficacy of reduction on the HCC incidence were 75%, 88%, 85%, 80% for those who aged 0-4, 5-9, 10-14, 15-19. They are quite similar to the previous reports. But for those young adults, the efficacy was attrition as 59% reduction in aged 20-24. This phenomenon might be affected by complete vaccination rate, the sustaining protection or carryover efficacy of HBV vaccination that might be varied by individual, for example, newborn with high transmission rate of e-antigen positive HBV carriers (Wu et al., 2013), different areas (Chen et al., 2015) with different horizontal transmission rate.

6.4 Cost-effectiveness analysis of different intervention strategies

While considering the economic appraisal of universal strategies vaccination is always cost-saving in comparison with other strategies because its effectiveness not only protect infection but also reduce the chance of having chronic liver disease. The latter may involve enormous indirect costs. Moreover, as the protection starts from birth, the gain for life years would be more than that gained from other strategies.

From the aspect of practice, a universal vaccination program against hepatitis B infection is not only effective for reducing long-term sequelae but is also a cost-saving

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primary preventive strategy, which supports a universal infant immunization in endemic area with high prevalence of HBV and HBeAg.

The effectiveness of anti-viral therapy is favourable but the cost seems still too high to make this strategy still not cost-saving but cost-effective within acceptable range.

It can be seen that the sole use of screening seems not cost-effective. This is because, from the viewpoint of economics, population-based screening has pros and cons. The greatest merit from population-based screening is to reduce a large proportion of deaths from HCC through early detection of diseases. However, time horizon for the benefit accrued from screening is later than cost incurred in initial screening. This aspect is more crucial in determination of costs for the comparison of the screened group with the unscreened group particularly when there is a long disease natural history form infection until HCC death.

It could be argued that whether mass screening or two-stage approach is used. Mass screening using AUS is more cost effective than two-stage biomarker-ultrasound screening. The most optimal strategies are an initial screening age at 50 years old and a two-year inter-screening interval.

These findings on CEA for universal approach support the adoption of various combinations of intervention programs particularly considering vaccination as the requisite as demonstrated in this thesis.

After anti-viral therapy, whether the schedule for surveillance should adjusted has been a common question. In this thesis, the risk stratification-based surveillance stratification approach suggesting more frequent AUS for the high risk group (5% of the target population) and infrequent for low-risk group (75% of the target population) had a 16-38% cost saved without compromising the efficacy of surveillance.

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Finally, in the era of early detection, providing the choice for different treatment decision like the use RFA or resected surgery is important for small HCC patients. Our economic appraisal for the comparison between RFA and resected surgery just hits the spot.

6.5 Methodological Considerations

As far as the methodology is concerned, the current thesis has developed an integrated and synthetic analytical decision framework as seen in the overall framework of Figure 3.1 to begin with the underlying susceptible population, experience through infectious and recovery process, suffer from chronic illness of the carrier, develop HCC, deteriorate into complications and finally succumb to death from HCC for the disease natural history in the absence of intervention program together with the current available treatments and therapies. Analytical decision tree structures embracing various intervention programs for interrupting the corresponding subsequent outcomes have been integrated into the framework as a unifying system for preventing HCC death. The development of such a systematic economic evaluation has several advantages from the aspect of methodology. The first merit is that the priority for various strategies can be taken when the resources are limited in accordance with the results of probabilistic CE plane and acceptability curves. In regard to primary and secondary prevention in the current thesis, universal vaccination against hepatitis vaccination can be prioritized as it is cost-saving. The second addition of intervention program is the administration of anti-viral therapy. The third consideration is pertaining to abdominal sonography screening. Second, the value of economic evaluation indicators such as ICERs and the likelihood of being cost-effective (LOBC) obtained from acceptability curve can be quantitatively compared across each strategy when they have the outcome such as HCC death in common. The third merit is that the marginal benefit in terms of cost and

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effectiveness of adding another intervention program given one intervention program can be quantitatively evaluated by using such a systematic economic evaluation framework.

6.6 Limitations

Geographic variation in HBV and HCV has never been considered and should be taken into account in the future when economic appraisal has been considered. Evidence-based information on efficacy of intervention is still lacking on the part of ant-viral therapy form Taiwanese data. This has been improved by having a longitudinal follow-up data. It had better consider the use of CBA analysis rather than only CEA analysis. Finally, optimal allocation of resources to various interventions should be developed in an quantitative manner when multiple intervention program have been considered.

6.7 Conclusions

In conclusion, this thesis has evaluated the effectiveness of reducing incidence and mortality of HCC by various intervention programs by using the empirical data on time-trend of epidemiology. Systematic economic appraisal for evaluation of various combinations of intervention programs have been done to show universal vaccination even in the combination with anti-viral therapy was always cost-saving screening. Optimal personalized surveillance for those with SVR seems available after the administration of anti-viral therapy. Such systematic economic appraisal is very helpful for the country with the same scenario of hepatitis virus infection in Taiwan when various combinations of intervention programs have been considered.

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Table 4. 1 Outcomes parameters for primary and secondary intervention for HCC

Variable	Estimate	Distribution Applied	Reference
Prevalence of hepatitis B infection in pregnant women			
Prevalence of HBsAg+ in pregnant women	0.095	Beta (10.28, 97.91)	Edmunds et al., 1996
Prevalence of HBeAg+ in HBsAg+ mother	0.458	Beta (6.1547, 7.2835)	Edmunds et al., 1996; Del Canho et al., 1997
Disease natural history related to hepatitis B virus			Hung et al, 2014
Vertical transmission	0.4118	Beta (35, 50)	
Susceptible → Latent period	0.035	Gamma (129.96, 3715.23)	
Latent period → Acute viral replication	1.1106	Gamma (5.32, 4.79)	
Acute viral replication → Carrier	0.0476	Gamma (30.75, 645.68)	
Acute viral replication → Recovery	0.1195	Gamma (7.34, 530.28)	
Carrier→Recovery	0.0138	Gamma (77.95, 652.56)	
Complication of acute hepatitis B infection			
Symptomatic hepatitis	0.2588	Beta(66, 189)	McMahon et al., 1985; Shah et al., 1985
Fulminant hepatitis among symptomatic hepatitis	0.001, Age<20; 0.005, Age≥20		Tassopoulos et al., 1987
Mortality of fulminant hepatitis	0.63, Age<15 0.80, 15≤Age<45 0.93, Age≥45		Tassopoulos et al., 1987; Dupuy et al., 1975; Redeker, 1975
Outcome after asymptomatic B carrier			
CAH	0.0031	Gamma (26, 8440)	McMahon et al., 1990; Kocak et al., 1998; Nishida et al., 1982 (35-37)
Death	0.0348	Gamma (0.0888, 2.55)	Fattovich et al., 2003(53)
Outcome after chronic hepatitis B			
CAR	0.15		
Incidence of cirrhosis			
from carrier	0.0263	Gamma (63, 2400)	Liaw et al., 1988; Fattovich et al., 1991; Ikeda et al., 1998 (44-46
From chronic hepatitis B	0.0263	Gamma (63, 2400)	
HCC incidence [Age groups]			

doi:10.6342/NTU201703133

Variable	Estimate	Distribution Applied	Reference
From non-liver cirrhosis	0.0024 0.0101 0.0332 0.0627 0.0821	Gamma (1.2, 510) [30s] Gamma (12, 1190) [40s] Gamma (120, 3614) [50s] Gamma (560, 8928) [60s] Gamma (1500, 18280) [70+]	Cancer statistics.; Chen et al., 2002; Wu et al., 2009
From liver cirrhosis	0.0048 0.0109 0.0316 0.0817 0.1640	Gamma (0.46, 96) [30s] Gamma (2.4, 220) [40s] Gamma (20, 632) [50s] Gamma (134, 1640) [60s] Gamma (538, 3280) [70+]	
Annual transition rates from the PCDP to CP of HCC			
For Non-liver cirrhosis	0.3754 (0.157~ 0.595)	Gamma(11.3, 30.1)	Chen et al., 2002; Yu et al., 2004
For liver cirrhosis	0.6397 (0.21~ 1.06)	Gamma(8.7, 13.6)	
Compliance to prevention program			
Vaccine coverage rate	0.90	Beta (9000, 1000)	Chen et al., 1996; Lin et al., 1998
Antiviral therapy for HBV			
For non-liver cirrhosis	0.50	Beta (2000,2000)	
For liver cirrhosis	0.67	Beta (2000,1000)	
Antiviral therapy for HCV	0.67	Beta (2000,1000)	
Mass screening	0.80	Beta (24000, 6000)	Wun and Dickinson, 2003; Chen et al., 1995; Chen et al., 2004
Efficacy of prevention program			
Efficacy of vaccine plus HBIG	0.9744	Beta (190,5)	Beasley et al., 1983
Efficacy of Lamivudine for vertical transmission	0.95	Beta (107,18)/ Beta (136, 47)	17, 18
Anti-viral therapy of HBV			
in liver cirrhosis	0.6500	exp[Normal(-0.4308, 0.1685)]	Yang et al., 2009
in HCC	0.5900	exp[Normal(-0.5276,	Yang et al., 2009

doi:10.6342/NTU201703133

Variable	Estimate	Distribution Applied	Reference
		0.1615)]	
Anti-viral therapy of HCV in LC, HCC	0.3921	exp[Normal(-0.9363, 0.1800)]	
Performance of ultrasonography			
Sensitivity to Cirrhosis (%)	80	Beta (62, 15)	Kuo et al., 2007
Sensitivity to HCC	95	Beta (50, 1)	Chen et al., 1995
Specificity to HCC	70	Beta (9493, 4282)	Chen et al., 1995

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Table 4. 2 Cost estimates for primary and secondary intervention for HCC

Variable	Direct	Indirect	Ref.
Vaccine	36	24	Garuz et al., 1997; Bloom et al., 1993; Fendrick et al., 1999; Da Villa et al., 1999; Mangtani et al., 1995
HBIG	80		Garuz et al., 1997; Bloom et al., 1993; Fendrick et al., 1999
Lamivudine	156		
Acute infection–Symptomatic	1645	740	Bloom et al., 1993; Fendrick et al., 1999
Fulminant hepatitis	25625	2220	Bloom et al., 1993; Fendrick et al., 1999
Asymptomatic carrier	220	48	Fendrick et al., 1999
Chronic active hepatitis	2980	740	Bloom et al., 1993; Fendrick et al., 1999; Ginsberg et al., 1992
Compensated cirrhosis	31272	2220	Bloom et al., 1993; Fendrick et al., 1999
Decompensated cirrhosis	35982	8880	Bloom et al., 1993; Fendrick et al., 1999
Ultrasonography		26	BNHI
Screening time (hour)		0.5	Chen et al., 2002; Wu et al.1998
Person accompanied for screening		0	Chen et al., 2002; Wu et al.1998
Time spending for ultrasonography		4	Chen et al., 2002; Wu et al.,1998
Confirmation (U.S. $)			
Confirmation time (hour)		8	Wu et al.,1998
Person accompanied for confirmation		1	Wu et al.,1998
Triple–phase abdominal CT		148	BNHI
Ultrasonic guidance for biopsy		38.3	BNHI
Liver puncture		36	BNHI
Specimen examinations of pathology		51.2	BNHI
Treatment (U.S. $)			

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Variable	Direct	Indirect	Ref.
Initial Cost of HCC treatment		4892, Lognormal(8.28,0.53)	NTUH
Continuing cost of HCC treatment		4266, Lognormal(8.18,0.46)	NTUH
Incurable-cancer care (average)		5691, Lognormal(8.36,0.81)	NTUH
Inpatient hospitalization (Day)		15	NTUH
Inpatient recovered at home (Day)		15	Wu et al.,1998
Person accompanied for inpatient care		1.69	Wu et al.,1998
Outpatient time per visit (hr)		4	Wu et al.,1998
Outpatient visit per year		9.7	NTUH
Patient accompanied for outpatient visit		0.77	Wu et al.,1998
Inpatient of terminal care (day)		30	NTUH
Person accompanied for terminal care		1	Wu et al.,1998
Average GNP per person ($US)		16,664	
Average work per month (hr)		184	DGBAS
Production value per hour ($US)		7.6	DGBAS
Discount rate (%)		3	

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Table 5. 1 The relative risks for age, gender, and period on HCC incidence and mortality

Stratified	Variable	Classification	HCC Incidence aRR(95%CI)	HCC Mortality aRR(95%CI)
Age 0-29	Age group	0-4 vs. 25-29	0.25(0.22, 0.28)	0.15(0.13, 0.18)
		5-9 vs. 25-29	0.12(0.10, 0.14)	0.16(0.14, 0.19)
		10-14 vs. 25-29	0.15(0.13, 0.18)	0.20(0.17, 0.22)
		15-19 vs. 25-29	0.20(0.18, 0.23)	0.25(0.22, 0.28)
		20-24 vs. 25-29	0.41(0.37, 0.44)	0.43(0.39, 0.47)
	Gender	Male vs. Female	2.97(2.76, 3.21)	3.28(3.02, 3.56)
	Period	1979-1983 vs. 2005-2013	0.88(0.78, 1.00)	2.74(2.43, 3.10)
		1984-1994 vs. 2005-2013	1.16(1.06, 1.27)	2.45(2.20, 2.73)
		1995-2004 vs. 2005-2013	1.47(1.34, 1.61)	1.82(1.63, 2.03)
Age 30-49	Age group	30-34 vs. 45-49	0.17(0.16, 0.18)	0.16(0.16, 0.17)
		35-39 vs. 45-49	0.34(0.33, 0.35)	0.34(0.33, 0.35)
		40-44 vs. 45-49	0.59(0.58, 0.60)	0.58(0.57, 0.60)
	Gender	Male vs. Female	6.29(6.10, 6.48)	6.89(6.66, 7.14)
	Period	1979-1983 vs. 2005-2013	0.48(0.46, 0.51)	1.54(1.48, 1.61)
		1984-1994 vs. 2005-2013	0.78(0.76, 0.81)	1.47(1.42, 1.51)
		1995-2004 vs. 2005-2013	1.11(1.08, 1.14)	1.31(1.27, 1.35)

doi:10.6342/NTU201703133

Age 50-69	Age group	50-54 vs. 65-69	0.38(0.38, 0.39)	0.35(0.34, 0.35)
		55-59 vs. 65-69	0.59(0.58, 0.60)	0.53(0.52, 0.54)
		60-64 vs. 65-69	0.80(0.79, 0.81)	0.76(0.74, 0.77)
	Gender	Male vs. Female	2.85(2.81, 2.89)	3.37(3.32, 3.42)
	Period	1979-1983 vs. 2005-2013	0.27(0.26, 0.27)	0.92(0.90, 0.94)
		1984-1994 vs. 2005-2013	0.50(0.49, 0.51)	0.97(0.95, 0.99)
		1995-2004 vs. 2005-2013	1.01(1.00, 1.03)	1.19(1.17, 1.21)
Age 70+	Age group	70-74 vs. 80+	1.05(1.03, 1.07)	0.80(0.78, 0.81)
		75-79 vs. 80+	1.06(1.04, 1.08)	0.93(0.91, 0.95)
	Gender	Male vs. Female	1.66(1.63, 1.69)	1.79(1.76, 1.82)
	Period	1979-1983 vs. 2005-2013	0.09(0.08, 0.10)	0.51(0.48, 0.53)
		1984-1994 vs. 2005-2013	0.33(0.32, 0.34)	0.66(0.64, 0.67)
		1995-2004 vs. 2005-2013	0.77(0.76, 0.78)	0.88(0.86, 0.89)

aRR: adjusted relative risk

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Table 5. 2 Simulated results of comparison between different single modality programs for preventing HCC and no intervention

	No intervention	*Universal vaccination*	*Anti-viral therapy for HBV*	*Anti-viral therapy for HCV*	*Anti-viral therapy for HBV and HCV*	*Mass screening*
Events						
Acute infection	266,380	32,917	266,390	266,422	266,405	266,425
Hepatitis B carrier	74,911	9,257	74,899	74,930	74,928	74,927
Hepatitis C carrier	11,795	11,847	11,812	11,799	11,802	11,815
Chronic hepatitis B	3,998	493	4,030	4,021	4,051	4,000
Compensated LC	36,429	4,472	35,957	36,227	35,793	36,426
Decompensated LC	16,372	1,991	17,002	16,432	17,047	16,392
HCC cases	16,085	1,984	13,614	15,777	13,322	16,839
HCC, Stage 2+	13,523	1,665	11,445	13,261	11,209	9,151
HCC death	14,336	1,767	12,085	14,035	11,795	12,350
All causes of death	136,401	115,721	135,397	136,272	135,237	134,946
RR	(Reference)					
Acute infection		0.1236	1.0000	1.0002	1.0001	1.0002
		(0.108,0.1478)	(0.9986,1.0016)	(0.9985,1.0014)	(0.9986,1.0018)	(0.9984,1.002)
Chronic hepatitis B		0.1232	1.0080	1.0055	1.0133	1.0004
		(0.1021,0.1484)	(0.9682,1.062)	(0.9567,1.0436)	(0.9745,1.0611)	(0.9616,1.0502)
Compensated LC		0.1228	0.9870	0.9945	0.9825	0.9999

doi:10.6342/NTU201703133

	No intervention	*Universal vaccination*	*Anti-viral therapy for HBV*	*Anti-viral therapy for HCV*	*Anti-viral therapy for HBV and HCV*	*Mass screening*
		(0.1072,0.1484)	(0.9702,1.0002)	(0.9831,1.0114)	(0.9668,0.9981)	(0.9881,1.0155)
Decompensated LC		0.1216	1.0385	1.0036	1.0412	1.0012
		(0.106,0.1516)	(0.9954,1.0787)	(0.9791,1.0302)	(0.9961,1.0875)	(0.9767,1.0244)
HCC cases		0.1234	0.8464	0.9809	0.8282	1.0469
		(0.1076,0.1461)	(0.7505,0.9263)	(0.9589,1.0065)	(0.7322,0.9108)	(1.0184,1.078)
HCC, Stage 2+		0.1231	0.8464	0.9807	0.8289	0.6767
		(0.1072,0.1444)	(0.7493,0.925)	(0.9538,1.0027)	(0.73,0.9105)	(0.6333,0.819)
HCC death		0.1233	0.8430	0.9790	0.8228	0.8615
		(0.1076,0.1471)	(0.7466,0.9215)	(0.9536,0.9984)	(0.7275,0.9044)	(0.7984,0.9433)
All causes of death		0.8484	0.9926	0.9991	0.9915	0.9893
		(0.8004,0.8895)	(0.984,1.0002)	(0.9926,1.0044)	(0.982,0.9996)	(0.9807,0.9977)

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Table 5. 3 Simulated results of different multiple modality programs for preventing HCC compared with no intervention and universal vaccination

	No intervention	*Universal vaccination*	*Universal vaccination + Anti-viral therapy*	*Universal vaccination + Mass screening*	*Universal vaccination + Mass screening + Anti-viral therapy*
Events					
Acute infection	266,380	32,917	32,868	32,895	32,859
Hepatitis B carrier	74,911	9,257	9,257	9,257	9,248
Hepatitis C carrier	11,795	11,847	11,824	11,818	11,819
Chronic hepatitis B	3,998	493	495	495	497
Compensated LC	36,429	4,472	4,395	4,481	4,386
Decompensated LC	16,372	1,991	2,071	1,995	2,067
HCC cases	16,085	1,984	1,647	2,089	1,725
HCC, Stage 2+	13,523	1,665	1,386	1,140	969
HCC death	14,336	1,767	1,459	1,531	1,259
All causes of death	136,401	115,721	115,565	115,581	115,441
RR_1	(Reference)				
Acute infection			0.1234 (0.1083,0.1473)	0.1235 (0.1083,0.1478)	0.1234 (0.1065,0.1485)
Chronic hepatitis B			0.1238 (0.1026,0.1485)	0.1238 (0.1032,0.1518)	0.1242 (0.0783,0.1905)
Compensated LC			0.1206 (0.1043,0.1438)	0.1230 (0.107,0.1494)	0.1204 (0.0796,0.1738)
Decompensated LC			0.1265 (0.109,0.1567)	0.1218 (0.1075,0.1488)	0.1262 (0.0569,0.2347)
HCC cases			0.1024 (0.0842,0.1251)	0.1299 (0.1117,0.1557)	0.1073 (0.0626,0.1731)
HCC, Stage 2+			0.1025 (0.084,0.1252)	0.0843 (0.0713,0.1118)	0.0717 (0.044,0.1169)
HCC death			0.1018 (0.0826,0.1249)	0.1068 (0.0891,0.1313)	0.0878 (0.0511,0.1435)
All causes of death			0.8472 (0.798,0.8893)	0.8474 (0.7997,0.8884)	0.8463 (0.7935,0.889)

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	No intervention	*Universal vaccination*	*Universal vaccination + Anti-viral therapy*	*Universal vaccination + Mass screening*	*Universal vaccination + Mass screening + Anti-viral therapy*
RR_2		(Reference)			
Acute infection			0.9985 (0.9812,1.0131)	0.9993 (0.9863,1.0134)	0.9982 (0.8353,1.197)
Chronic hepatitis B			1.0045 (0.8837,1.1371)	1.0048 (0.8867,1.1682)	1.0076 (0.6008,1.6764)
Compensated LC			0.9828 (0.9448,1.0272)	1.0021 (0.9653,1.0427)	0.9809 (0.5669,1.4564)
Decompensated LC			1.0398 (0.9852,1.111)	1.0017 (0.9552,1.061)	1.0379 (0.4529,1.9144)
HCC cases			0.8301 (0.7214,0.9315)	1.0526 (0.9912,1.1393)	0.8695 (0.4985,1.4328)
HCC, Stage 2+			0.8323 (0.7312,0.9334)	0.6847 (0.6172,0.8287)	0.5820 (0.3551,0.9435)
HCC death			0.8254 (0.7197,0.9349)	0.8661 (0.7677,0.9671)	0.7124 (0.4095,1.1455)
All causes of death			0.9986 (0.9925,1.0042)	0.9988 (0.993,1.0051)	0.9976 (0.9834,1.0092)

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Table 5. 4 Cost-effectiveness analysis among different single modality for the primary and secondary prevention of HCC

	No intervention	*Universal vaccination*	*Anti-viral therapy for HBV*	*Anti-viral therapy for HCV*	*Anti-viral therapy for HBV and HCV*	*Mass screening*
Cost	25,108	3,091	25,582	25,119	25,594	25,417
Life-year	65.91	67.85	65.99	65.93	66.01	66.00
Incremental cost		-22,017.03	473.69	11.56	485.98	309.40
Incremental effectiveness		1.9425	0.0787	0.0219	0.0946	0.0931
ICER		-11,334 (-18110, -5704)	6,017 (-6561, 32815)	527 (-16480, 58799)	5,137 (672,22245)	3,323 (-1339, 16002)

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Table 5. 5 Cost-effectiveness analysis among different combined modality for the primary and secondary prevention of HCC

	No intervention	*Universal vaccination*	*Universal vaccination + Anti-viral therapy*	*Universal vaccination + Mass screening*	*Universal vaccination + Mass screening + Anti-viral therapy*
Cost	25,108	3,091	3,145	3,205	3,252
Life-year	65.91	67.85	67.86	67.86	67.87
(vs No intervention)					
Incremental cost			-21,963	-21,903	-21,855
Incremental effectiveness			1.9542	1.9523	1.9603
ICER			-11,239 (-18000,-5710)	-11,219 (-17776,-5723)	-11,149 (-18262,-5571)
(vs Vaccine only)					
Incremental cost			54	114	162
Incremental effectiveness			0.0116	0.0098	0.0177
ICER			4,633 (-33414,34875)	11,668 (-58164,31715)	9,102 (-103320,33628)

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Table 5. 6 Cost-effectiveness analysis between RFA and surgery for small HCC

	Surgery	*RFA*
Cost ($)	28306.20	29461.57
Life-year	5.4940	4.8708
Incremental cost ($)	-1155.37	
Incremental effectiveness	0.6231	
ICER	-1,854	

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Table 5. 7 Estimated results of the cost-effectiveness analysis for the AUS surveillance for HCC among patients of chronic hepatitis C with SVR

Strategy	Cost,$	Effectiveness (LYG)	Compared with no surveillance			Compared with usual care		
			Incremental Cost ($)	Incremental LYG	ICER1	Incremental Cost ($)	Incremental LYG	ICER2
No surveillance	441.8	7.9907	Reference	Reference	Reference			---
Usual Care	1091.0	8.0049	649.2	0.0142	45718	Reference	Reference	Reference
RSBSS-1	674.7	7.9970	232.9	0.0063	36968	-416.3	-0.0079	52696
RSBSS-2	724.1	8.0001	282.3	0.0094	30032	-366.9	-0.0048	76438
RSBSS-3	753.4	7.9998	311.6	0.0091	34242	-337.6	-0.0051	66196
RSBSS-4	802.8	8.0029	361.0	0.0122	29590	-288.2	-0.0020	144100
RSBSS-5	914.5	8.0049	472.7	0.0142	33289	-176.5	0.0000	Cost-saving

RSBSS: risk stratification-based surveillance stratification
RSBSS-1: (High-risk group) 6-monthly；(Intermediate-risk group) 1-yearly；(Low-risk group) 2-yearly
RSBSS-2: (High-risk group) 3-monthly；(Intermediate-risk group) 1-yearly；(Low-risk group) 2-yearly
RSBSS-3: (High-risk group) 6-monthly；(Intermediate-risk group) 6-monthly；(Low-risk group) 2-yearly
RSBSS-4: (High-risk group) 3-monthly；(Intermediate-risk group) 6-monthly；(Low-risk group) 2-yearly
RSBSS-5: (High-risk group) 3-monthly；(Intermediate-risk group) 3-monthly；(Low-risk group) 1-yearly

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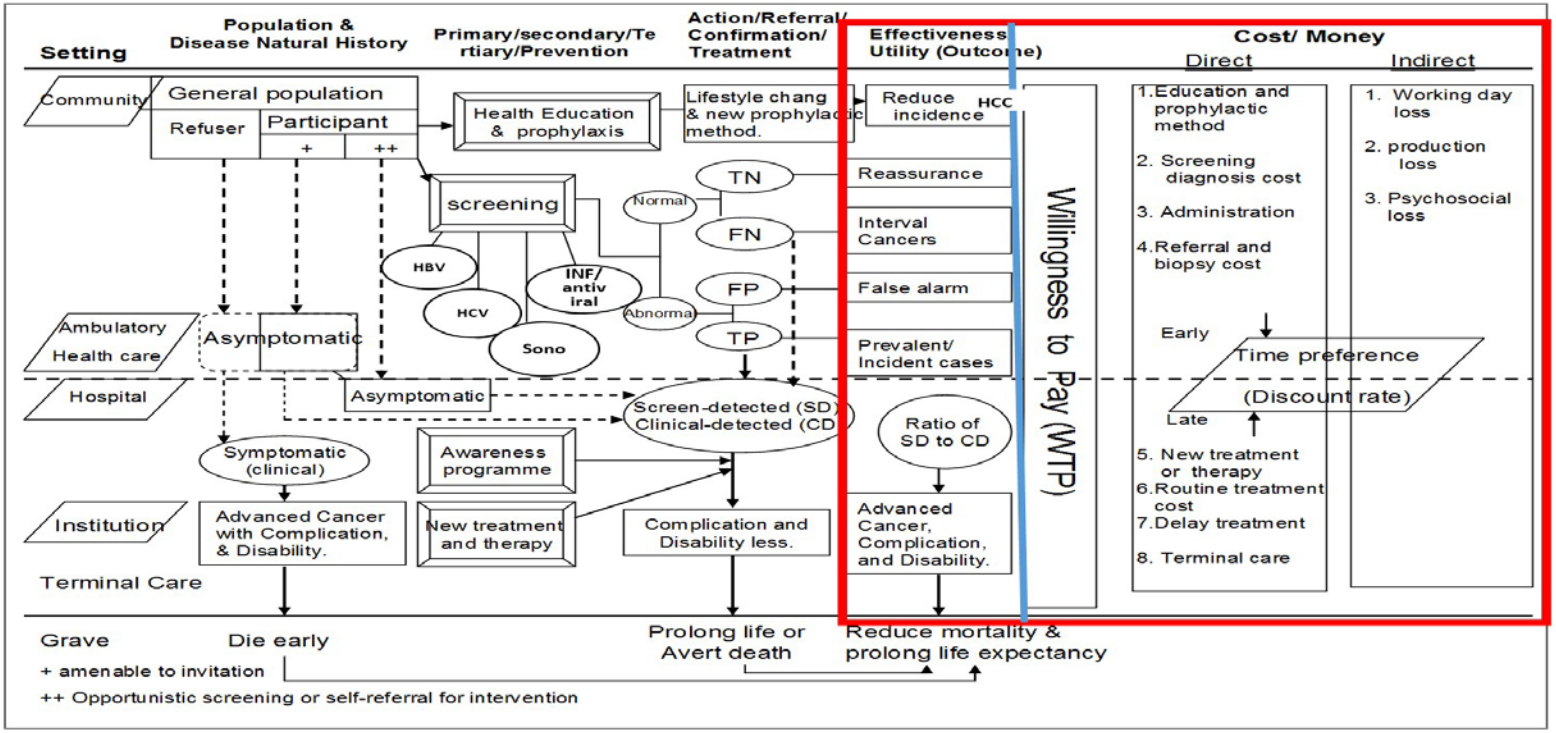
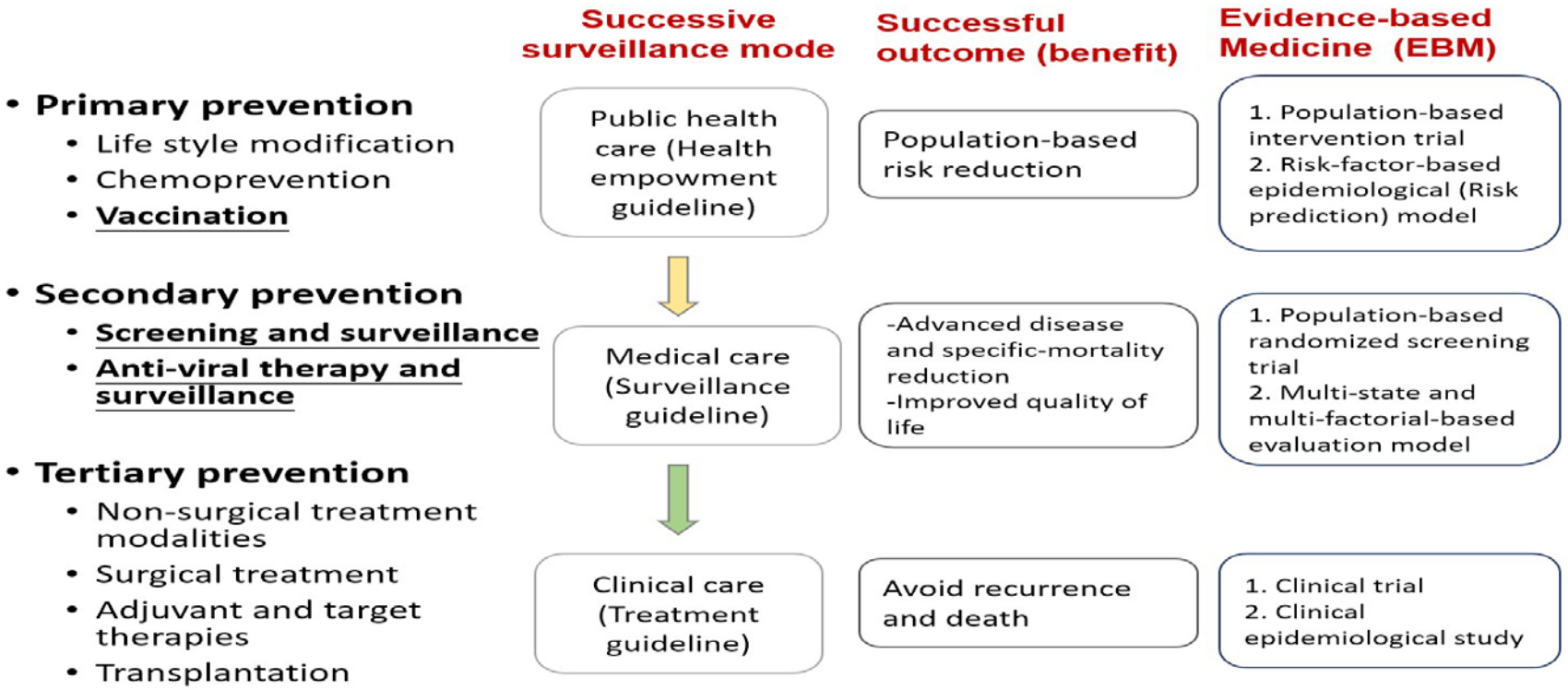
Figure 3. 1 shows the backbone of economic appraisal for intervention program of HCC



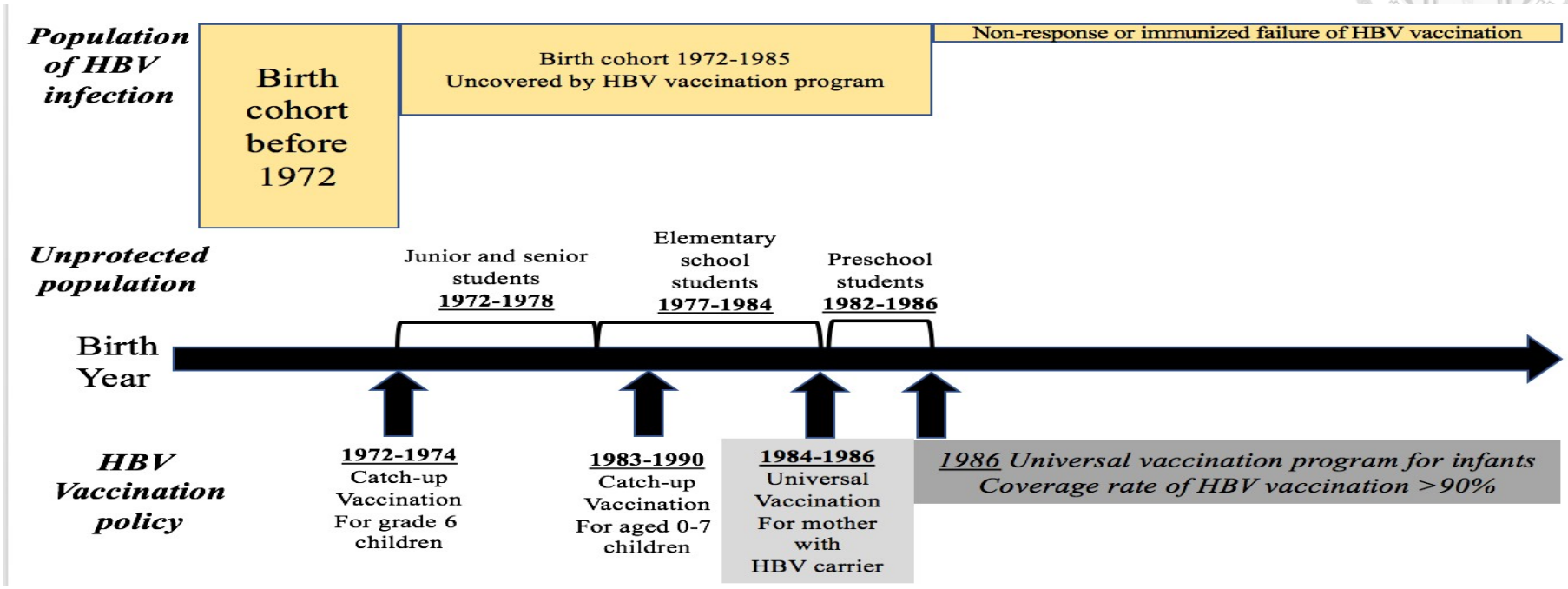
doi:10.6342/NTU201703133

Figure 3. 2 shows three levels of prevention, successive surveillance, and treatment and therapy of HCC in the light of EBM



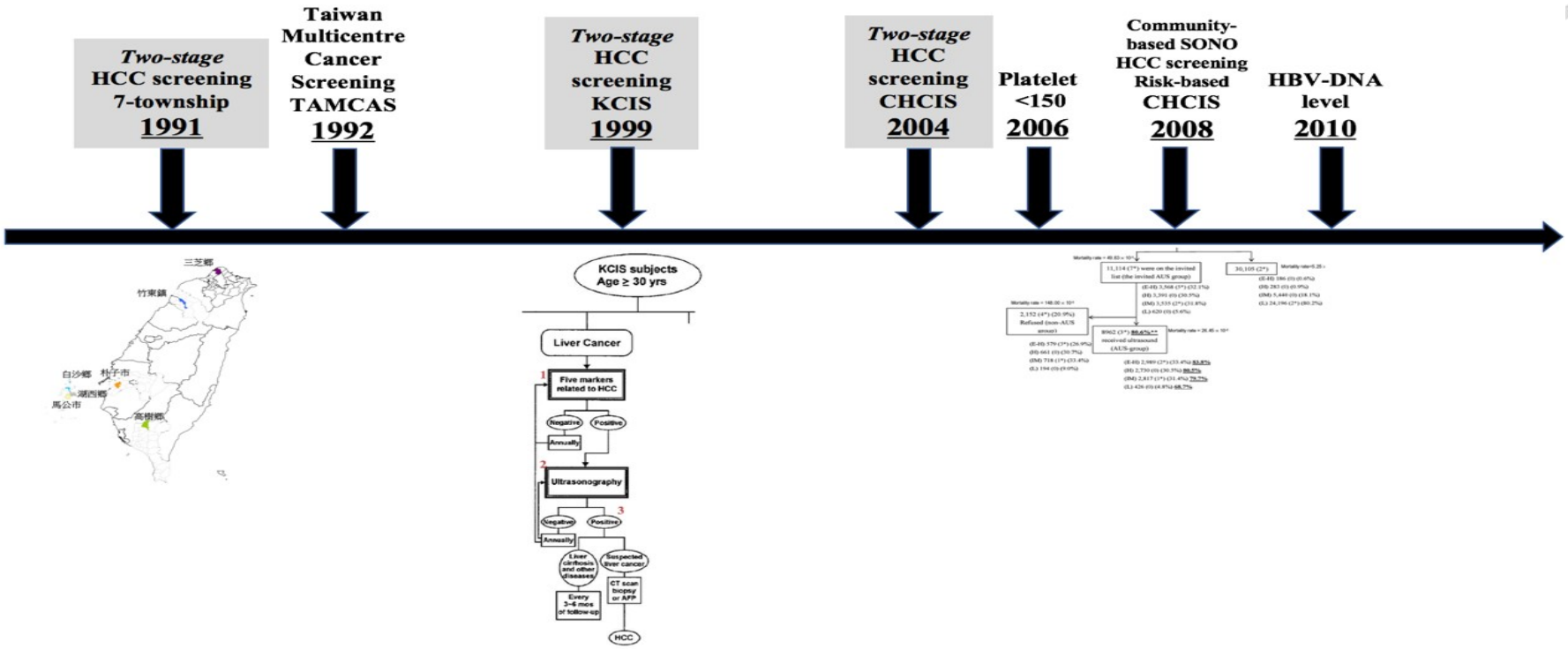
doi:10.6342/NTU201703133

Figure 3. 3 Universal HBV vaccination in Taiwan



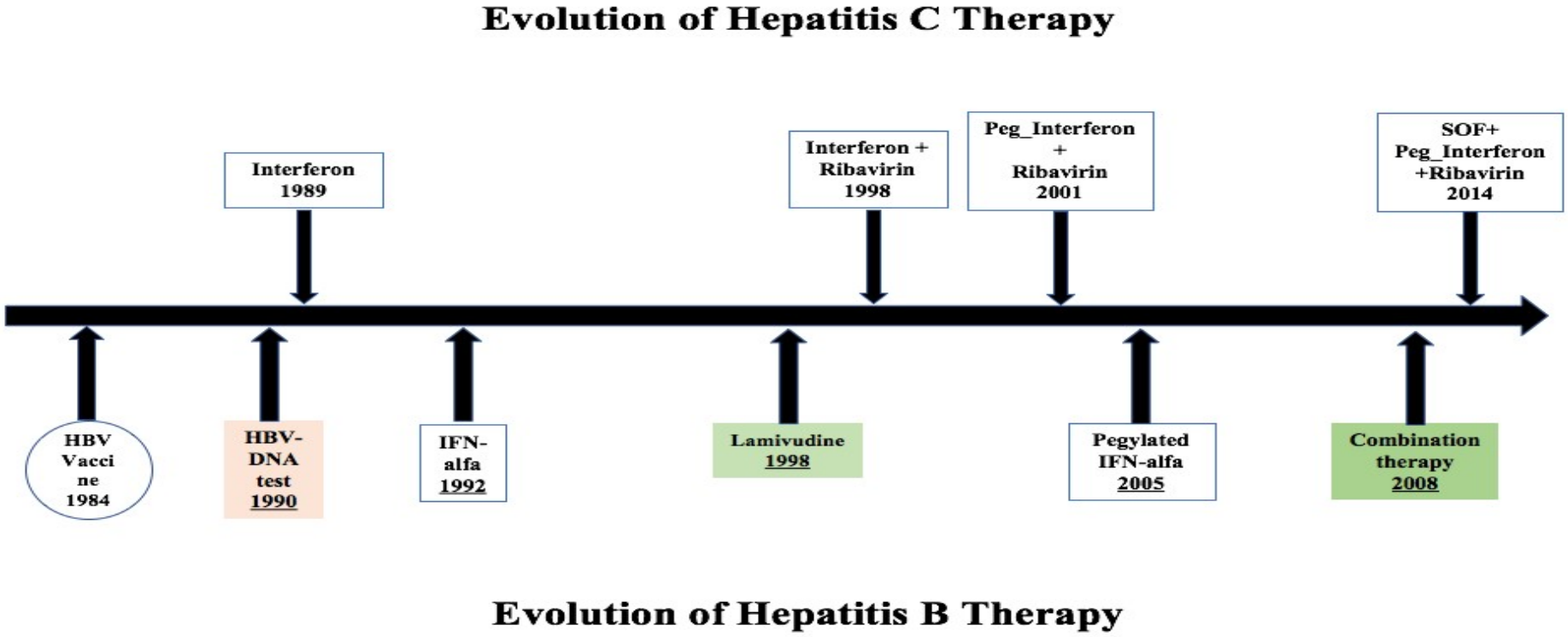
doi:10.6342/NTU201703133

Figure 3. 4 The evolution of HCC screening policy in Taiwan



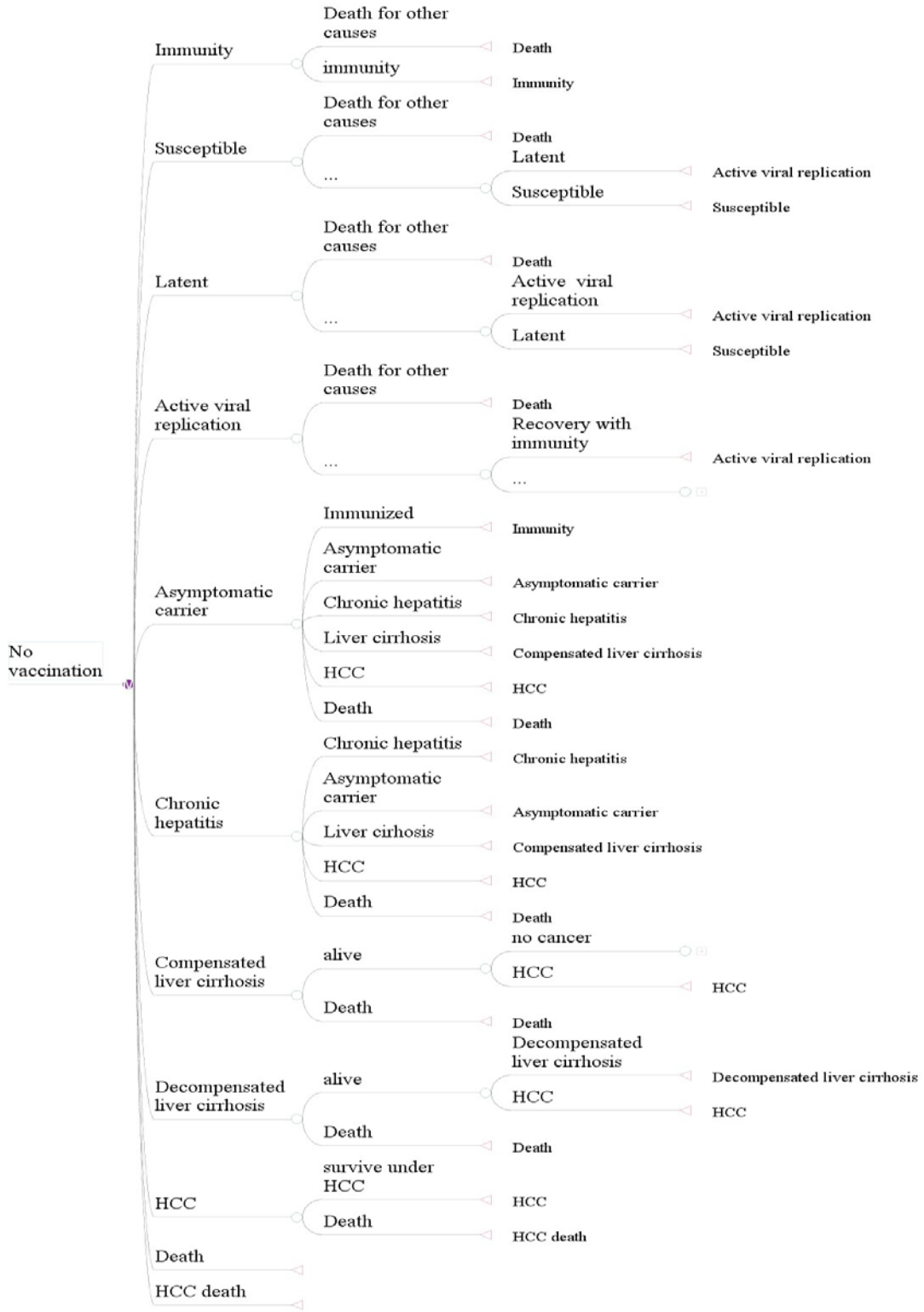
doi:10.6342/NTU201703133

Figure 3. 5 Anti-viral therapy for hepatitis B and C



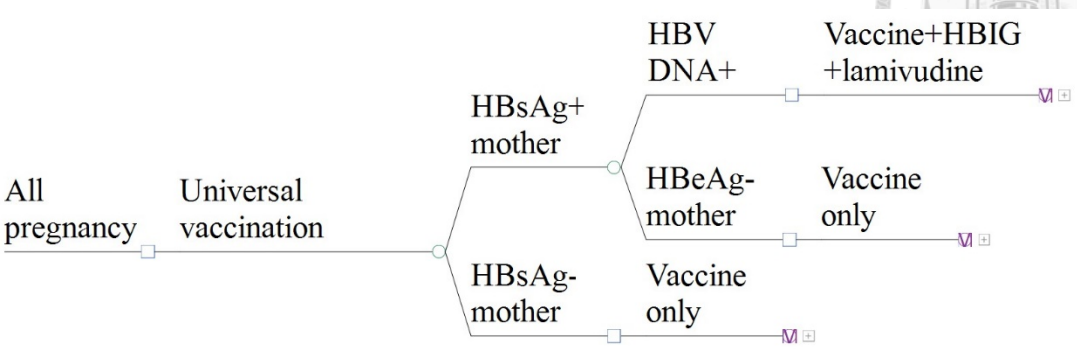
doi:10.6342/NTU201703133

Figure 4. 1 The Markov decision tree for the disease natural history of liver diseases without intervention



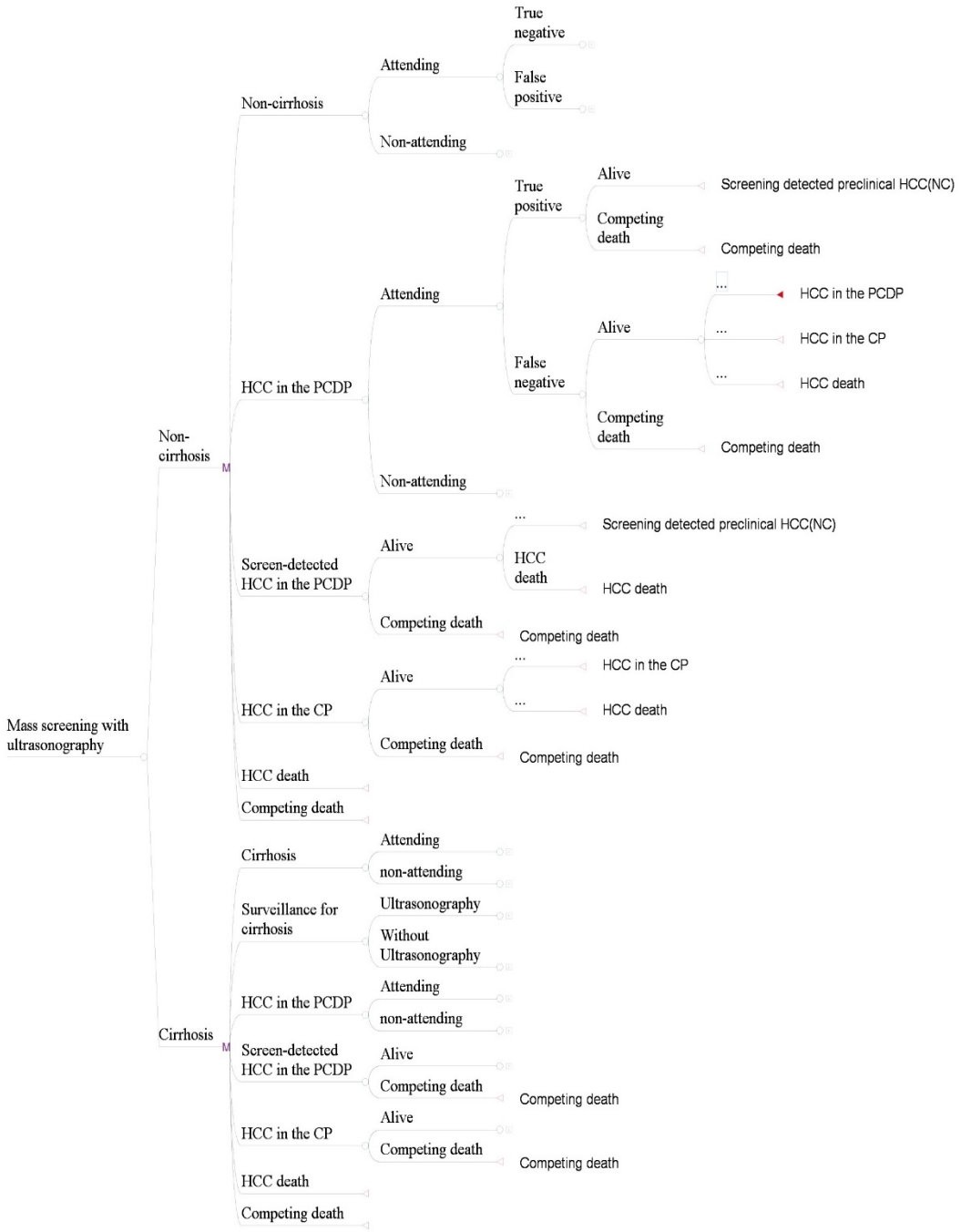
doi:10.6342/NTU201703133

Figure 4. 2 The decision tree for strategy of vaccination



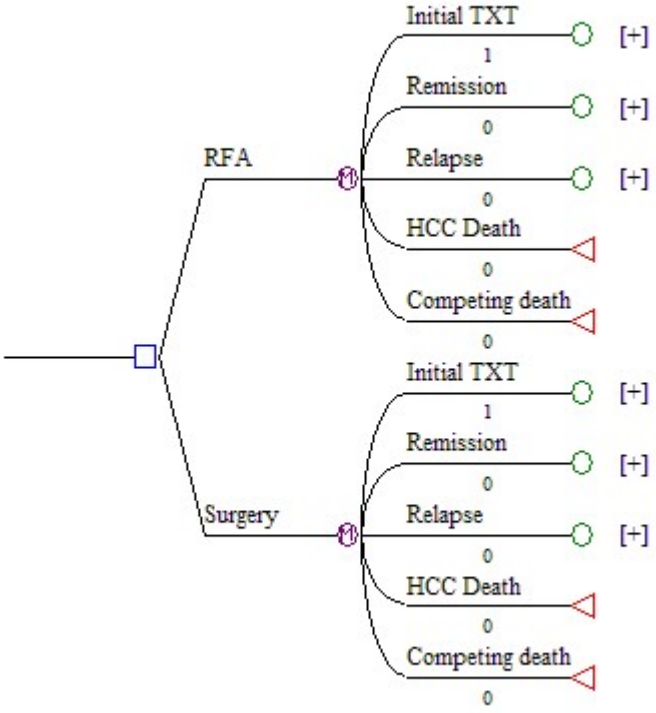
doi:10.6342/NTU201703133

Figure 4. 3 The Markov decision tree for mass screening for HCC with abdominal ultrasound



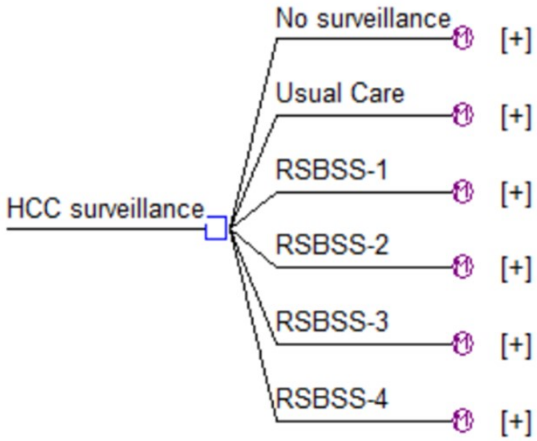
doi:10.6342/NTU201703133

Figure 4. 4 The Markov decision model for the choice of RFA and surgery among patients with small HCC



doi:10.6342/NTU201703133

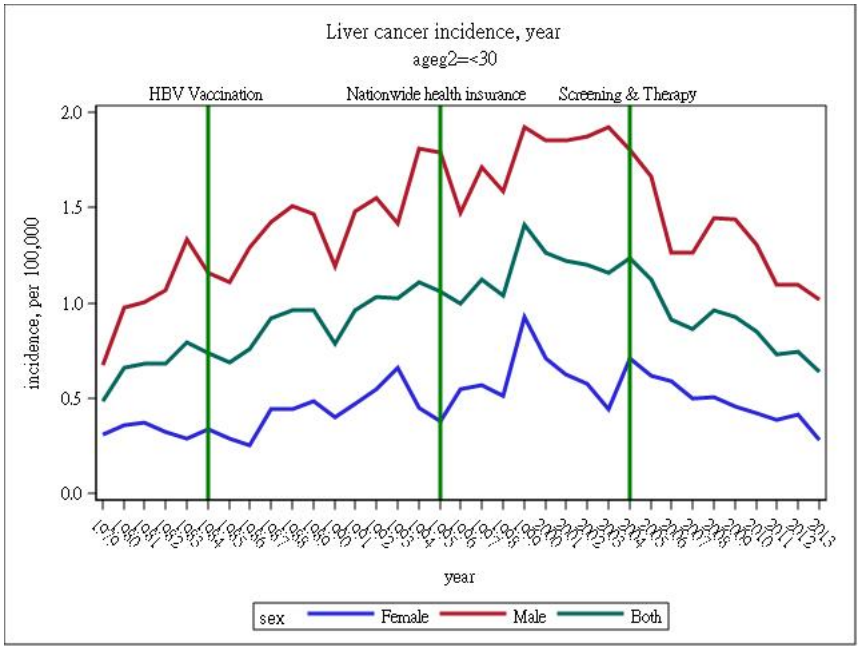
Figure 4. 5 The Markov decision model for the Personalized surveillance for patients with SVR in the era of the anti-viral therapy



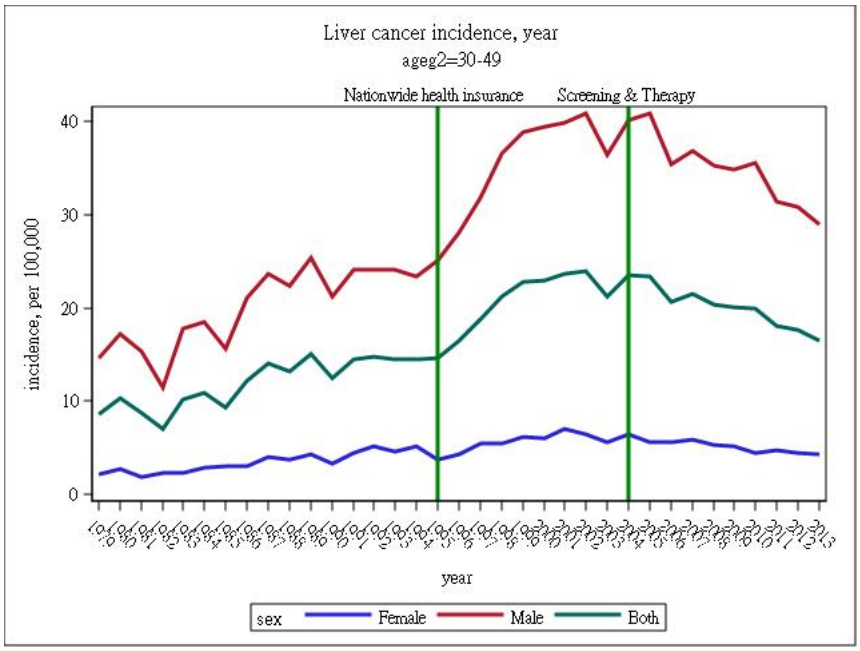
doi:10.6342/NTU201703133

Figure 5. 1 Secular trend of incidence (per 100,000) of HCC by gender and age group, Taiwan

(A) 0-29 years-old

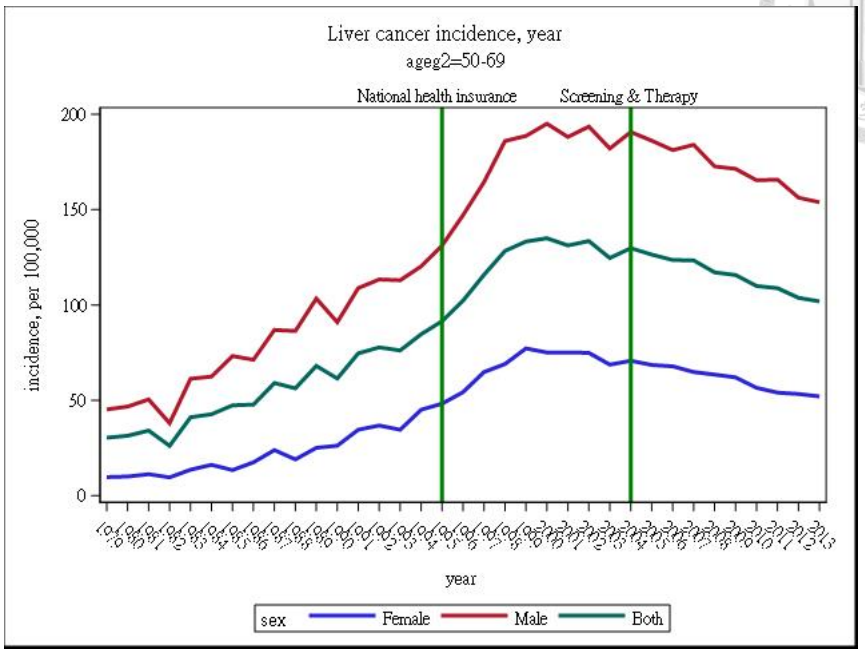


(B) 30-49 years-old

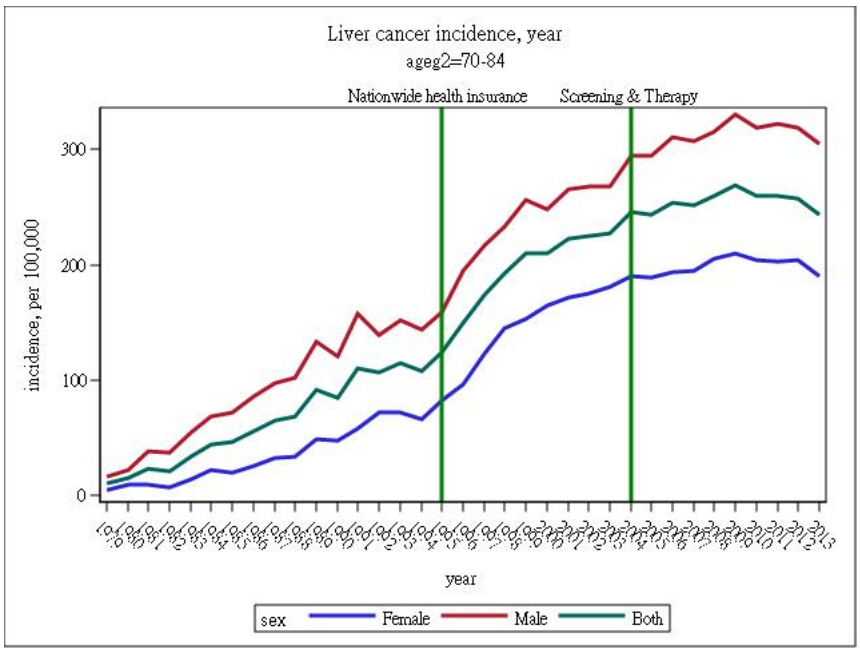


doi:10.6342/NTU201703133

(C) 50-69 years-old



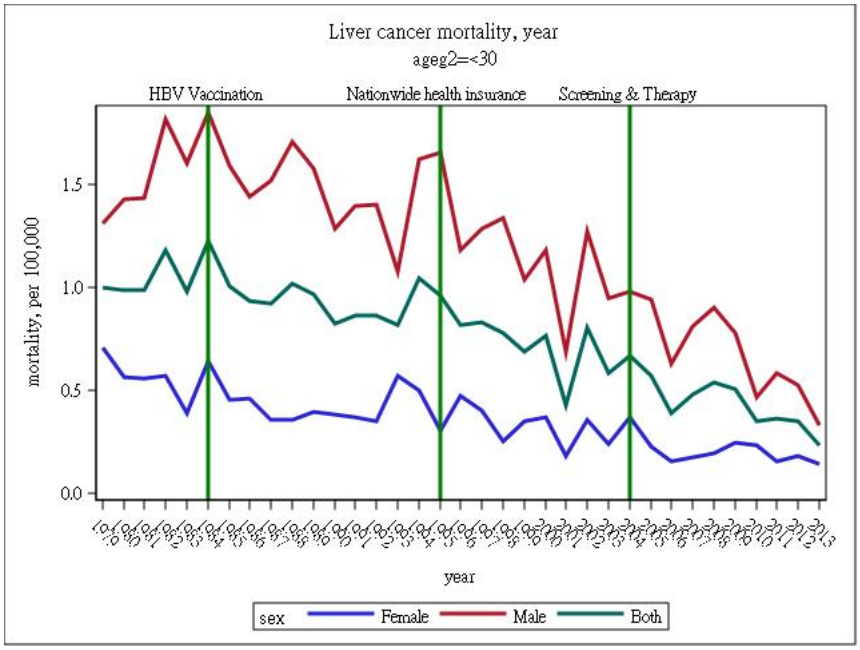
(D)70-84 years-old



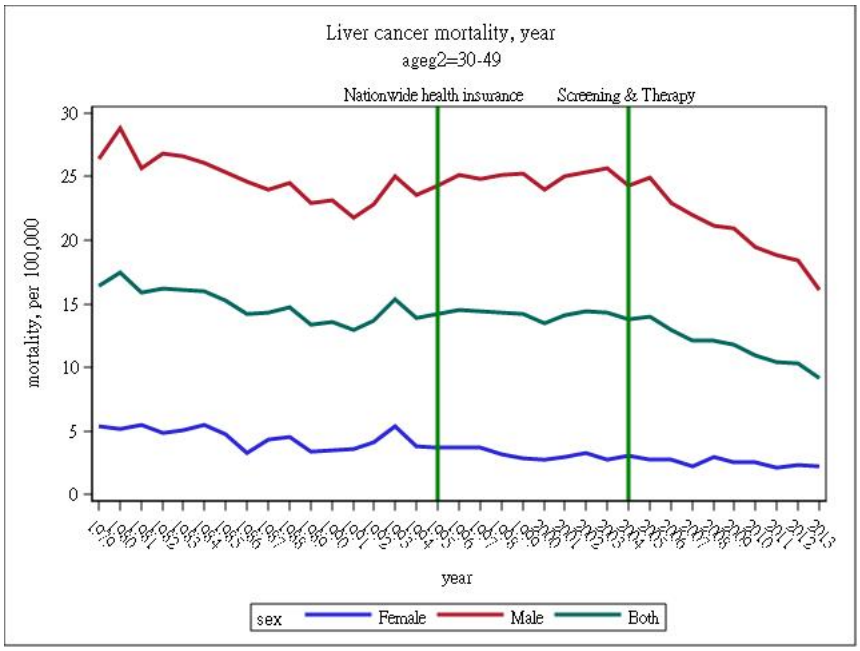
doi:10.6342/NTU201703133

Figure 5. 2 Secular trend of mortality (per 100,000) of HCC by gender and age group, Taiwan

(A)0-29 years-old



(B)30-49 years-old



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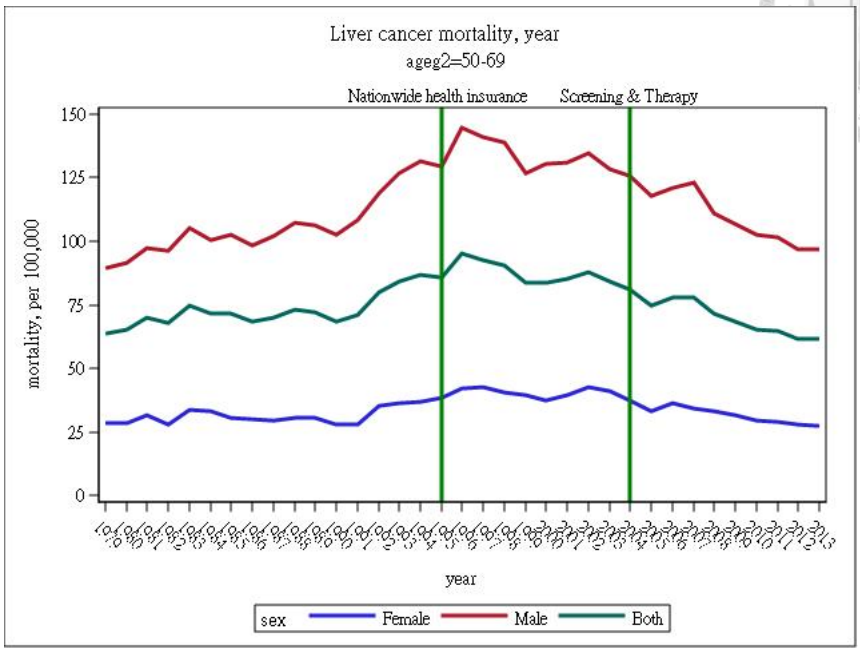
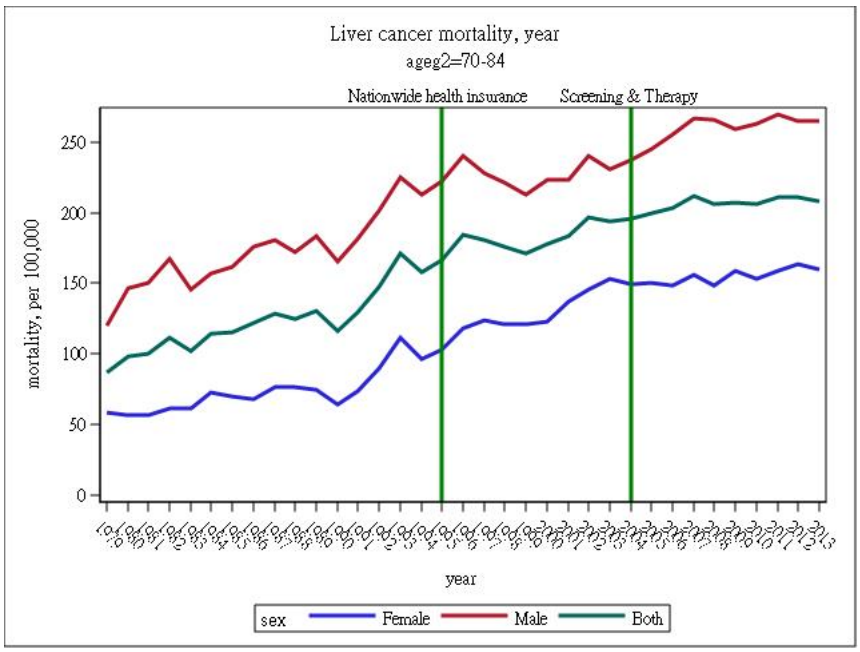
(C)50-69 years-old



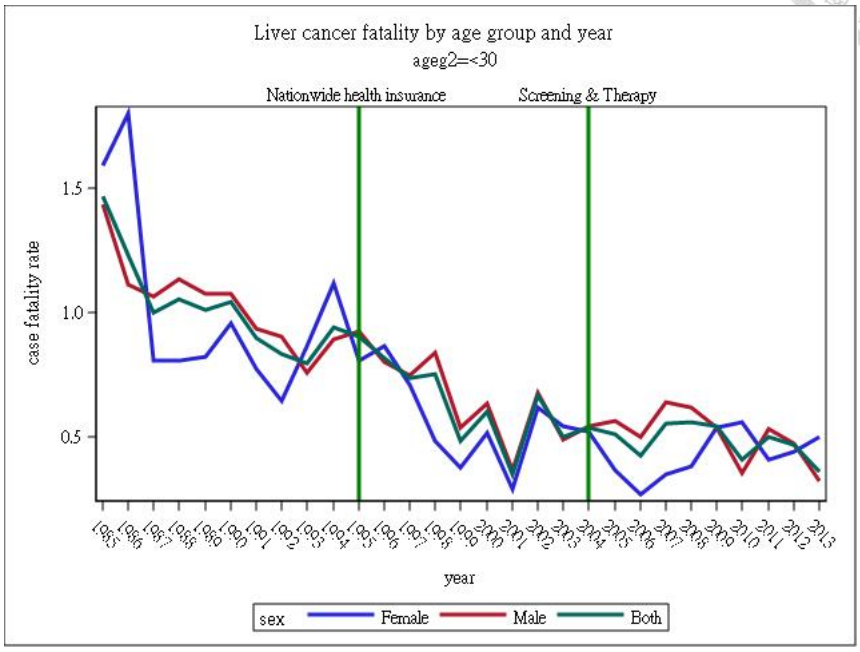
(D)70-84 years-old



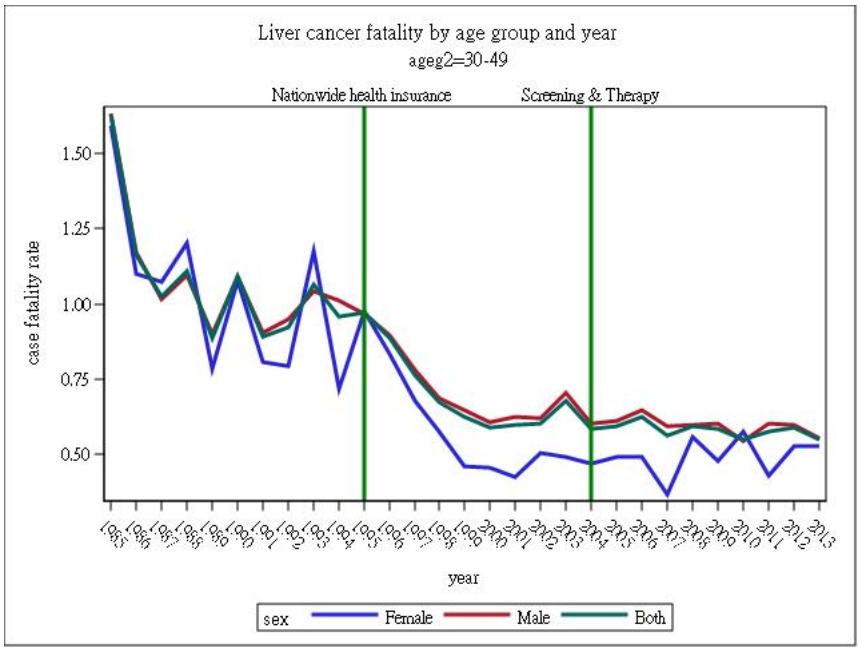
doi:10.6342/NTU201703133

Figure 5. 3 Secular trend of fatality rate of HCC by gender and age group, Taiwan

(A)0-29 years-old

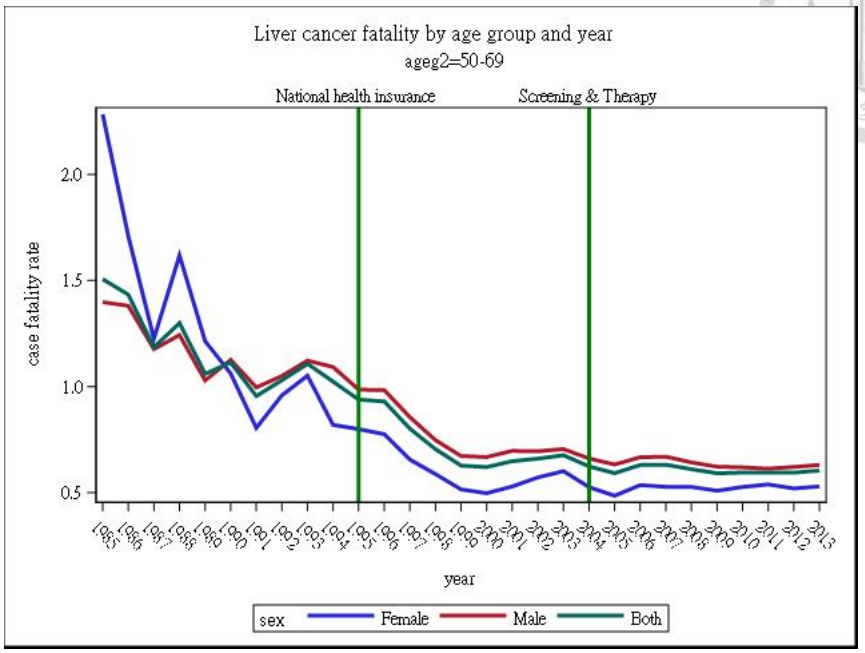


(B)30-49 years-old

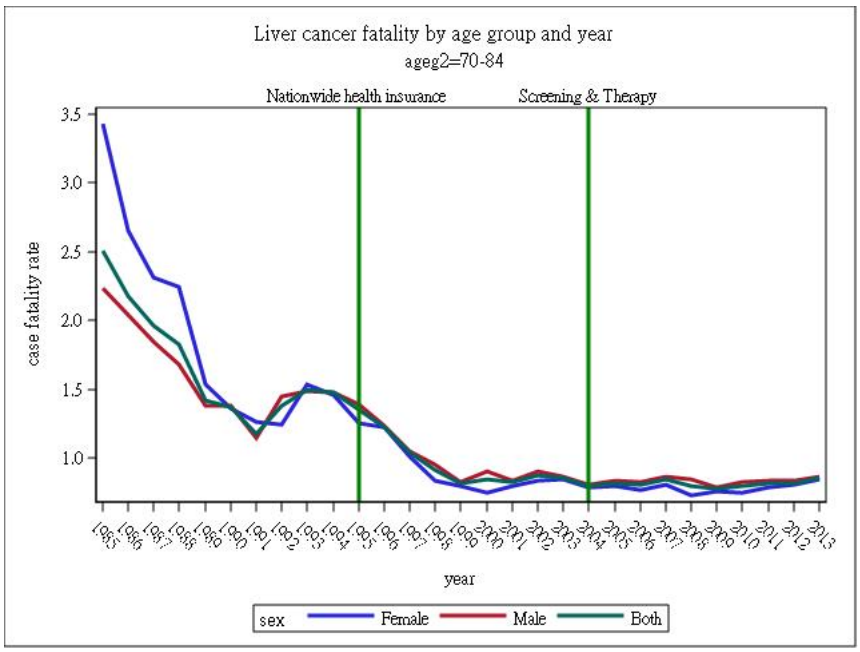


doi:10.6342/NTU201703133

(C)50-69 years-old



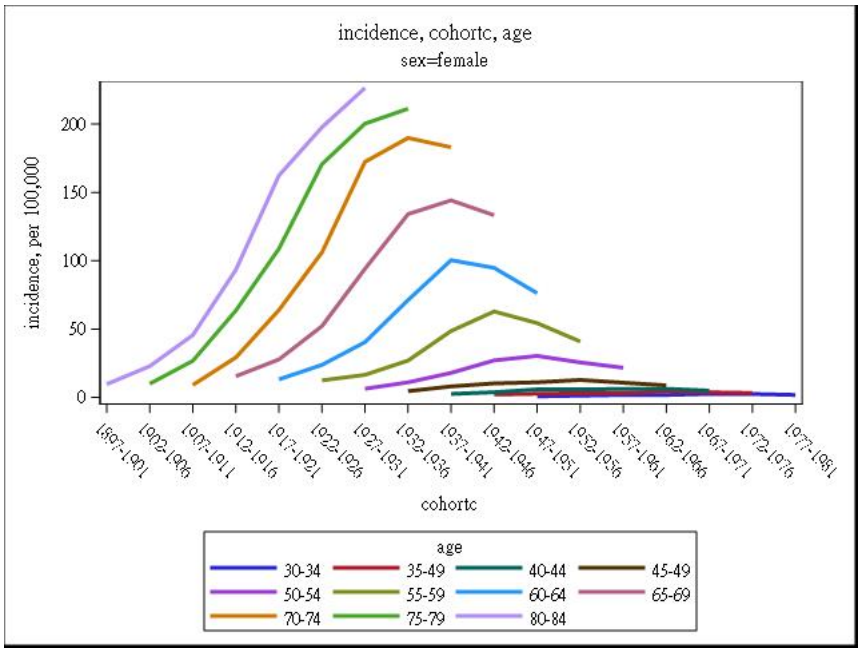
(D) 70-84 years-old



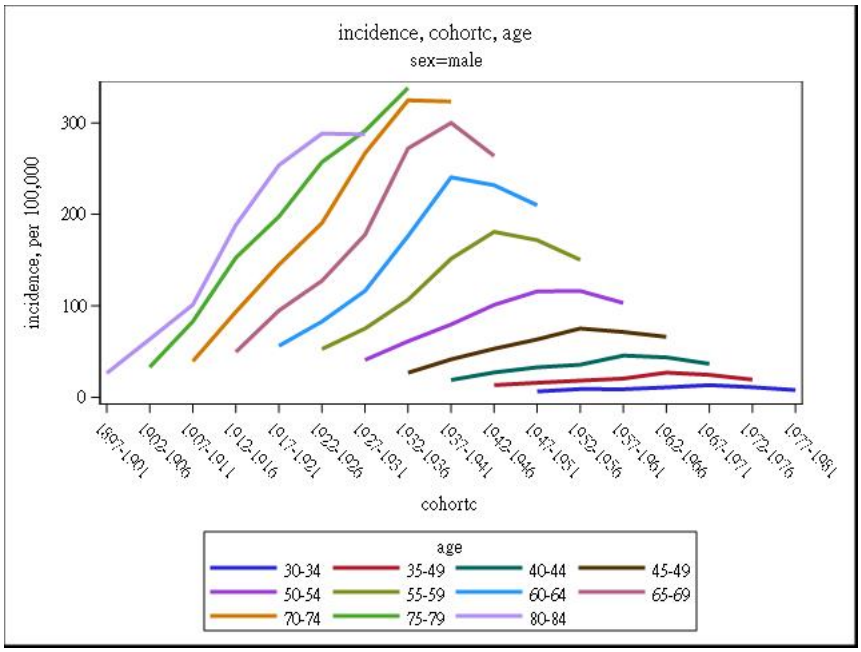
doi:10.6342/NTU201703133

Figure 5. 4 The age-cohort plot for HCC by gender, Taiwan

(A) Female



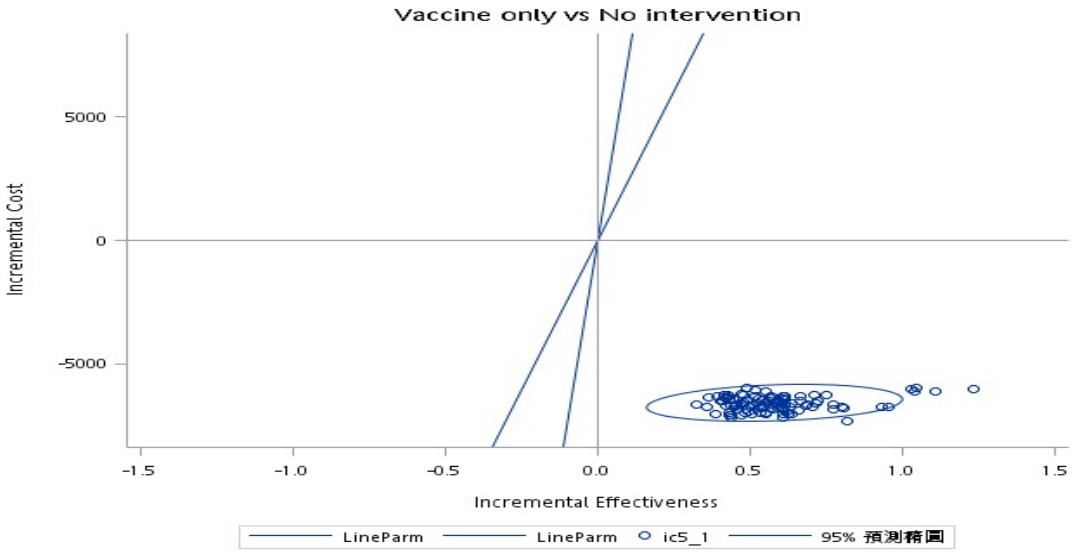
(B)Male



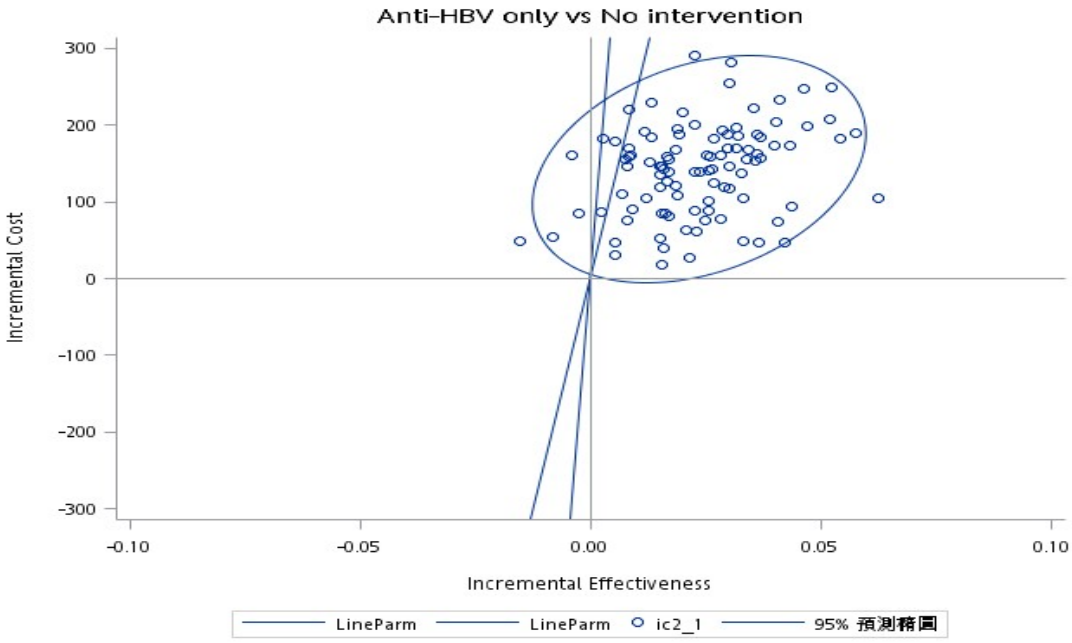
doi:10.6342/NTU201703133

Figure 5. 5 Scatter plot of incremental cost and incremental effectiveness for single modality of primary and secondary intervention for HCC compared to no intervention

(A) Universal Vaccination

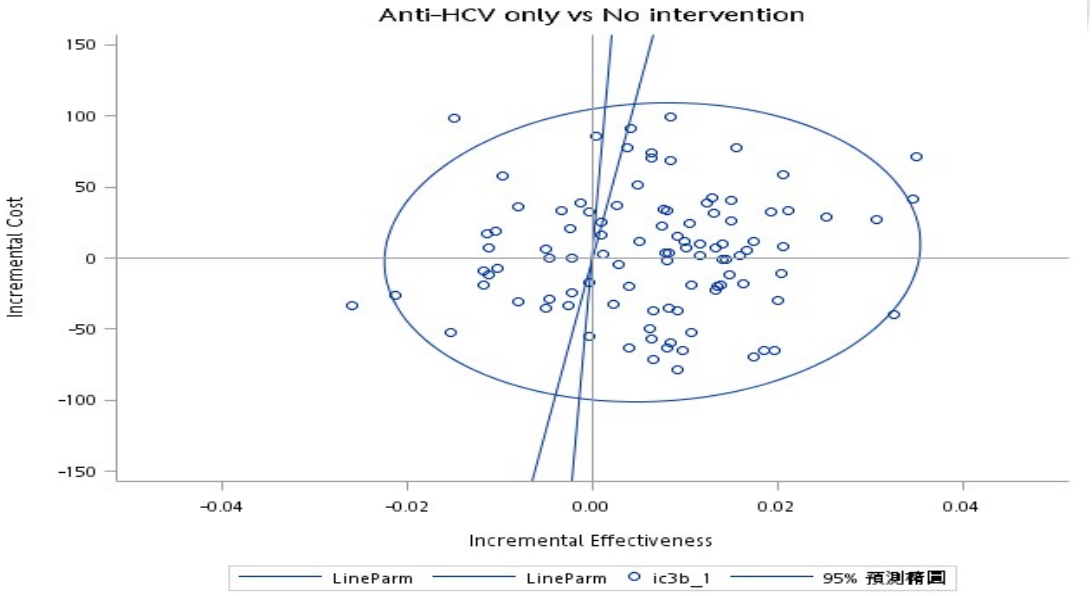


(B) Anti-HBV

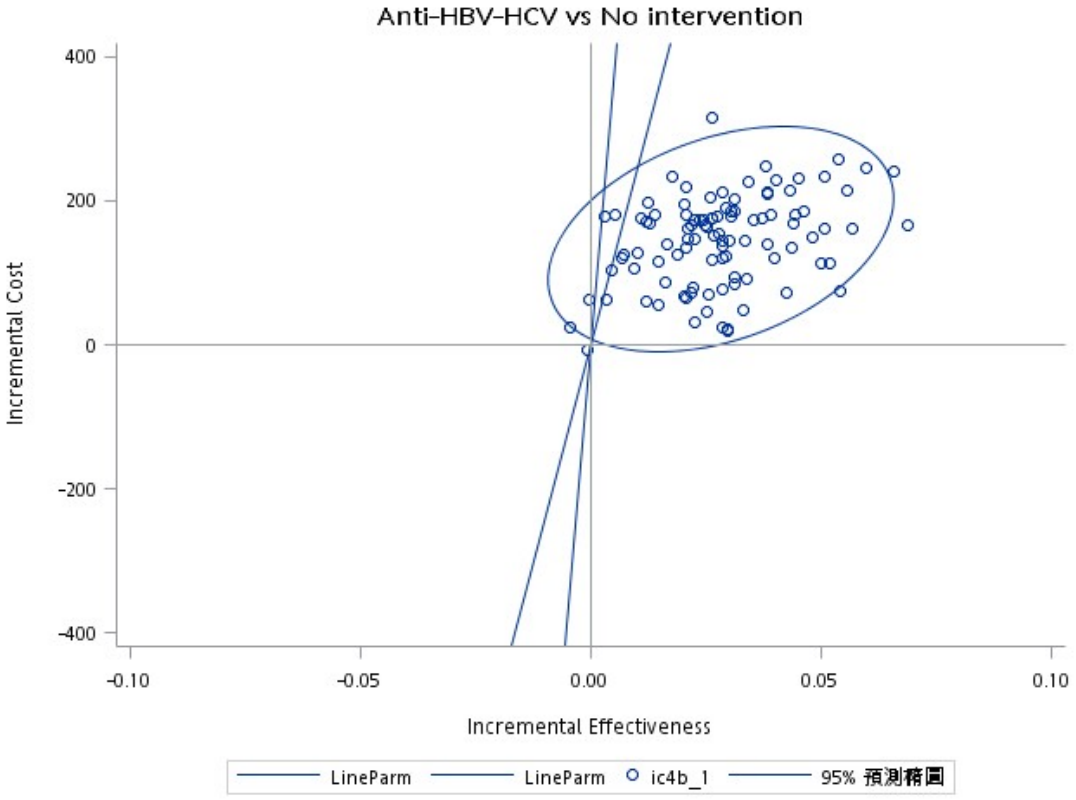


doi:10.6342/NTU201703133

(C) Anti-HCV

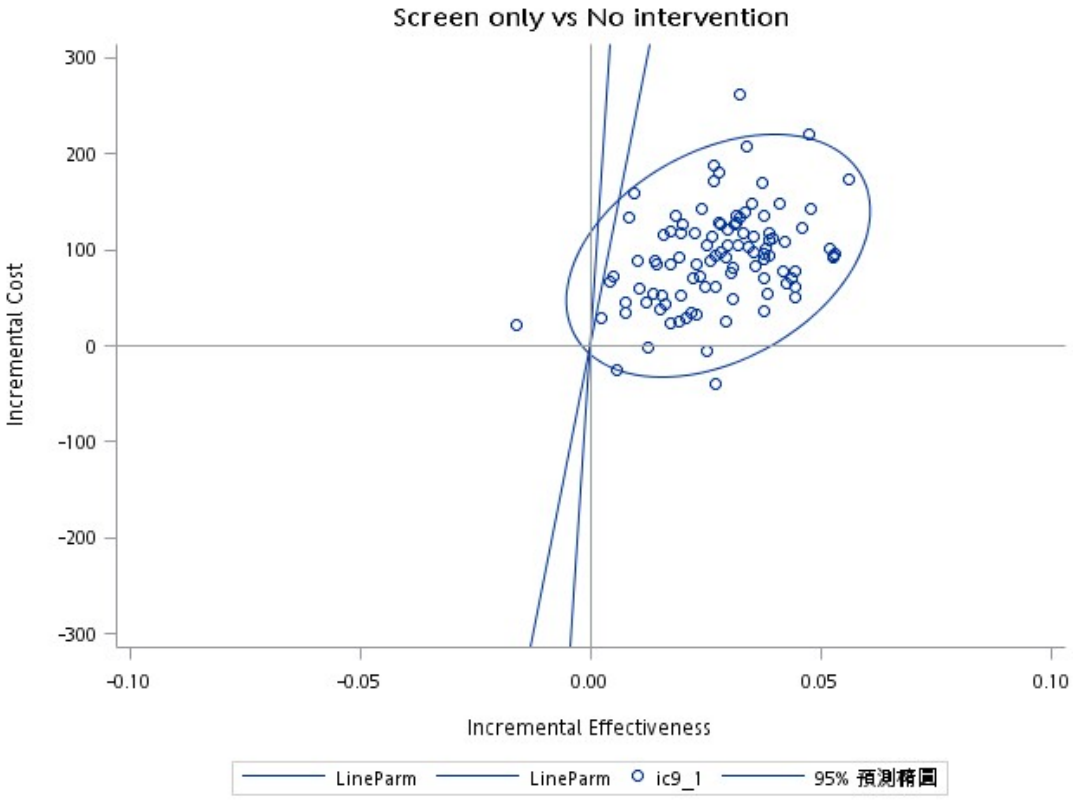


(D) Anti-HBV + Anti-HCV



doi:10.6342/NTU201703133

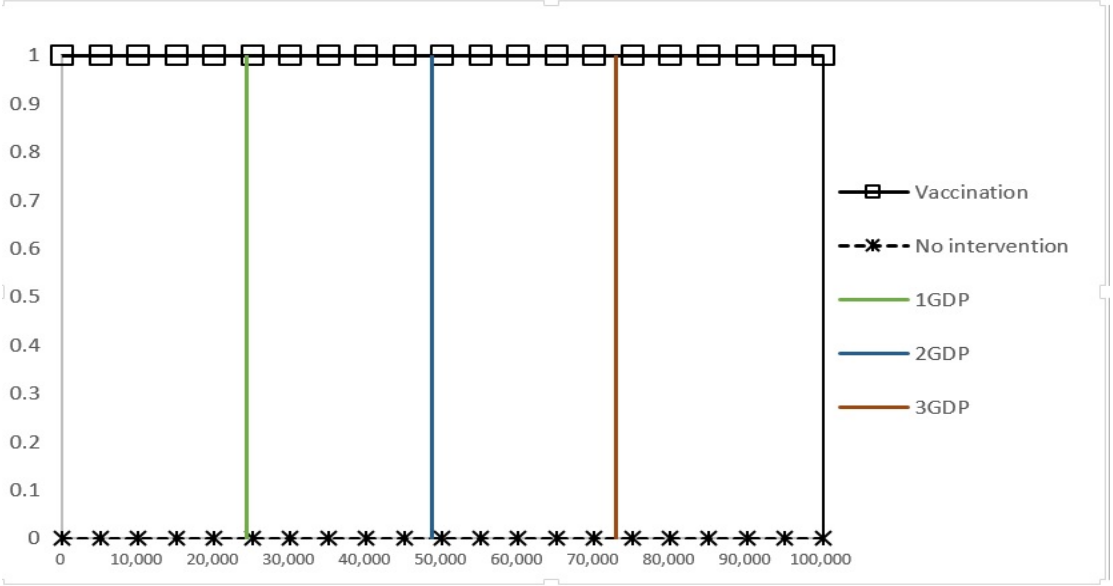
(E) Mass screening



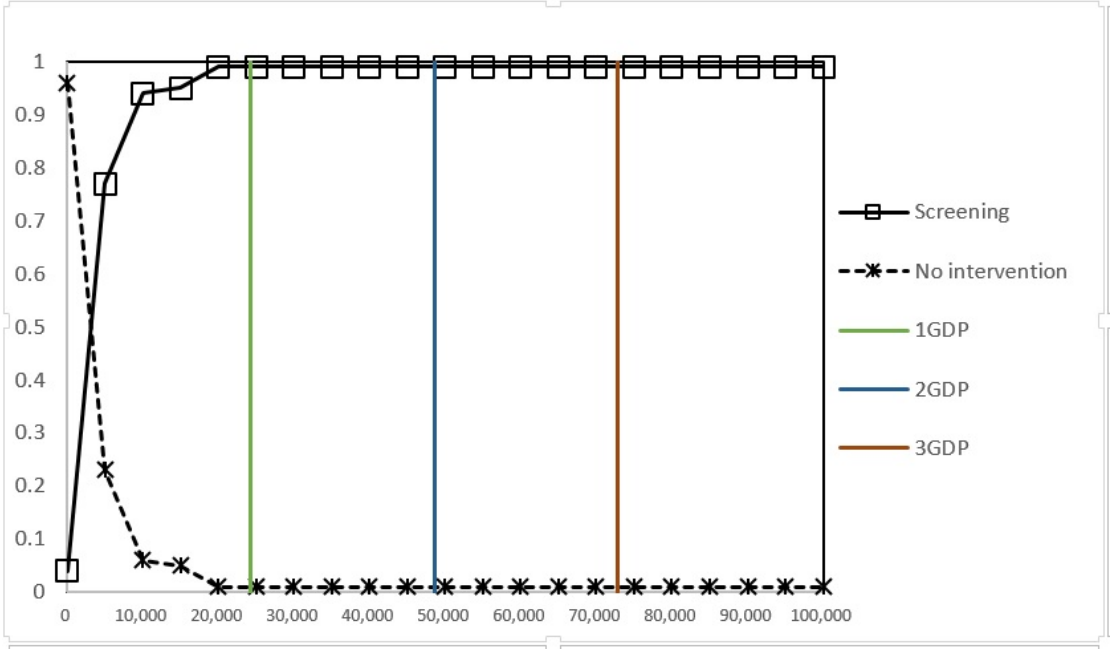
doi:10.6342/NTU201703133

Figure 5. 6 Acceptability cures for preventing HCC with single modality compared with no intervention

(A) Vaccination vs. No intervention

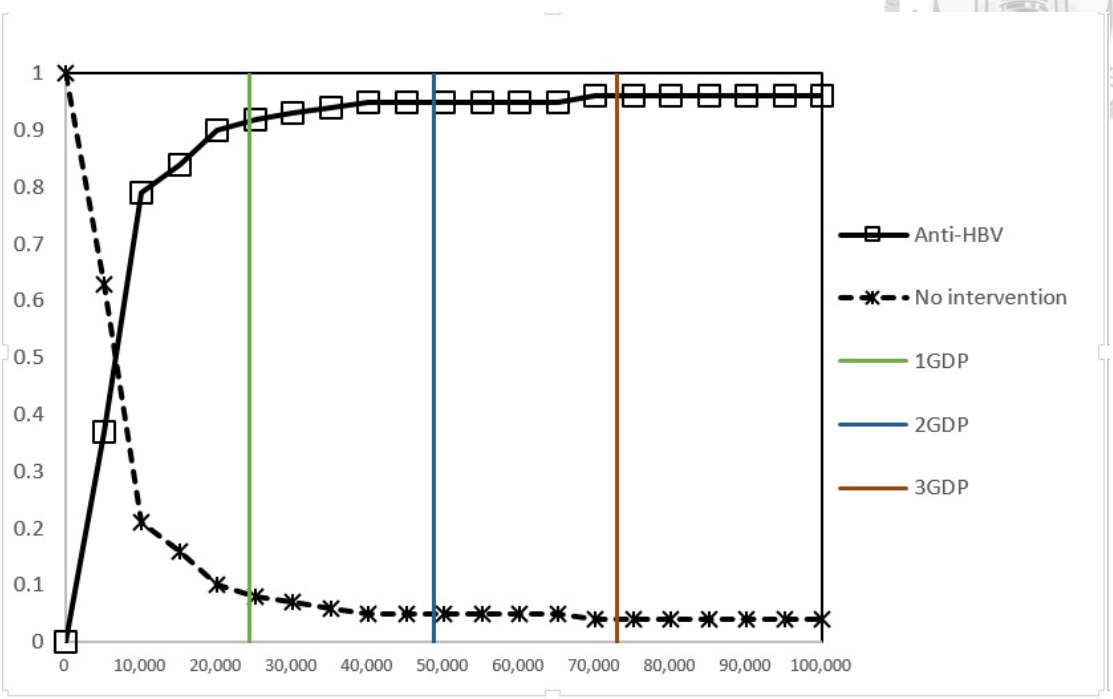


(B) Screening vs. No intervention

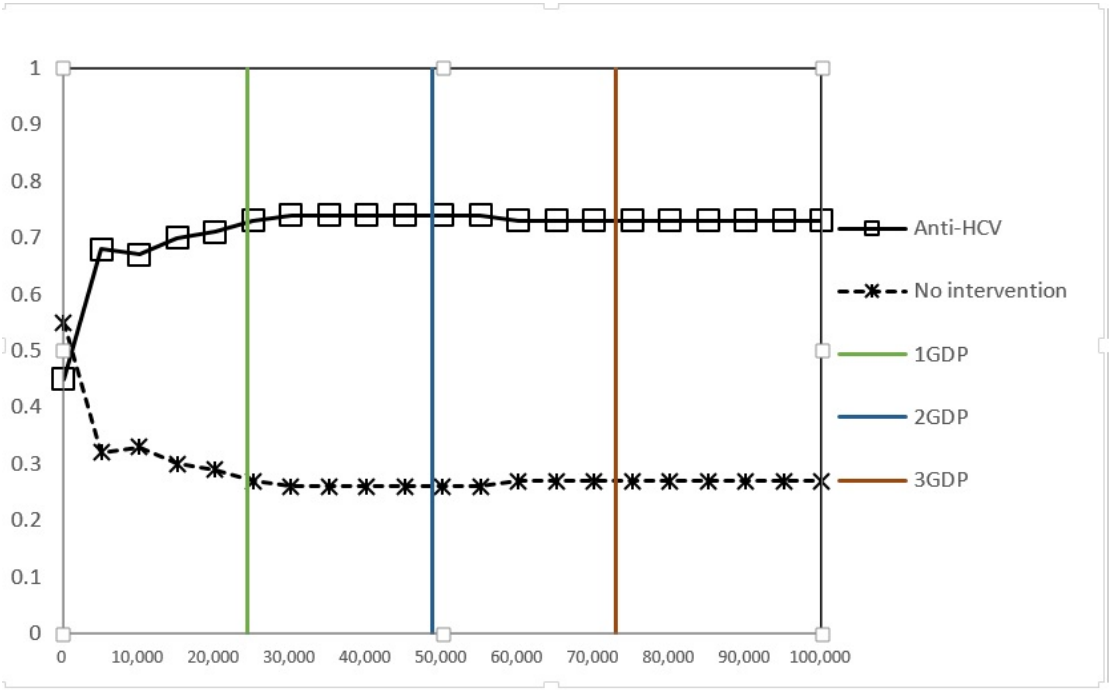


doi:10.6342/NTU201703133

(C) Anti-HBV vs. No intervention



(D) Anti-HCV vs. No intervention



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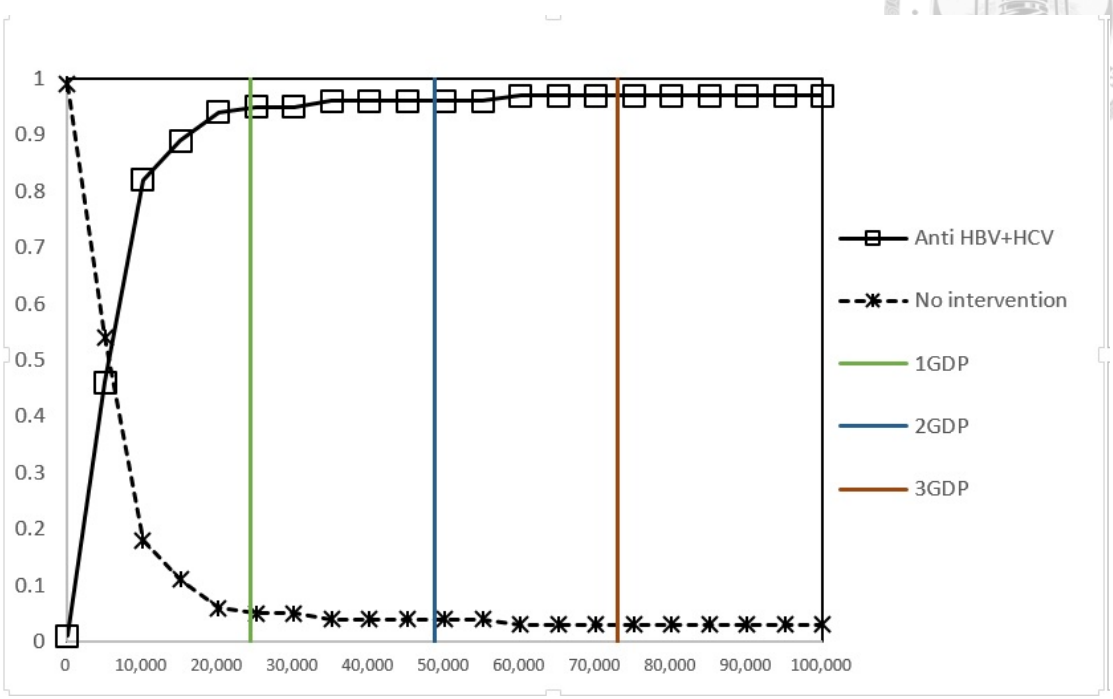
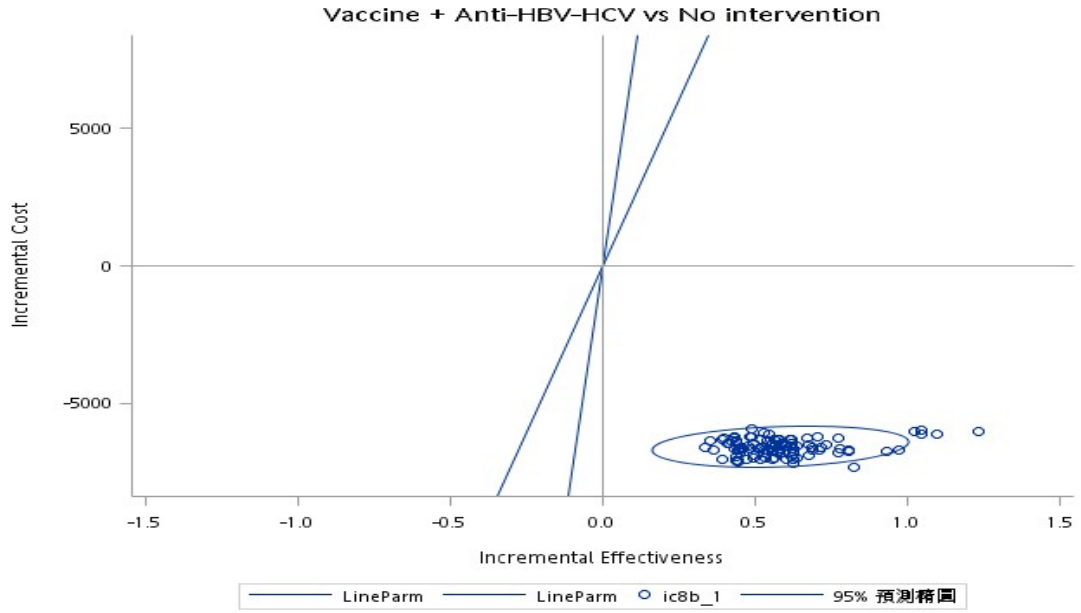
(E) Anti-HBC+HCV vs. No intervention



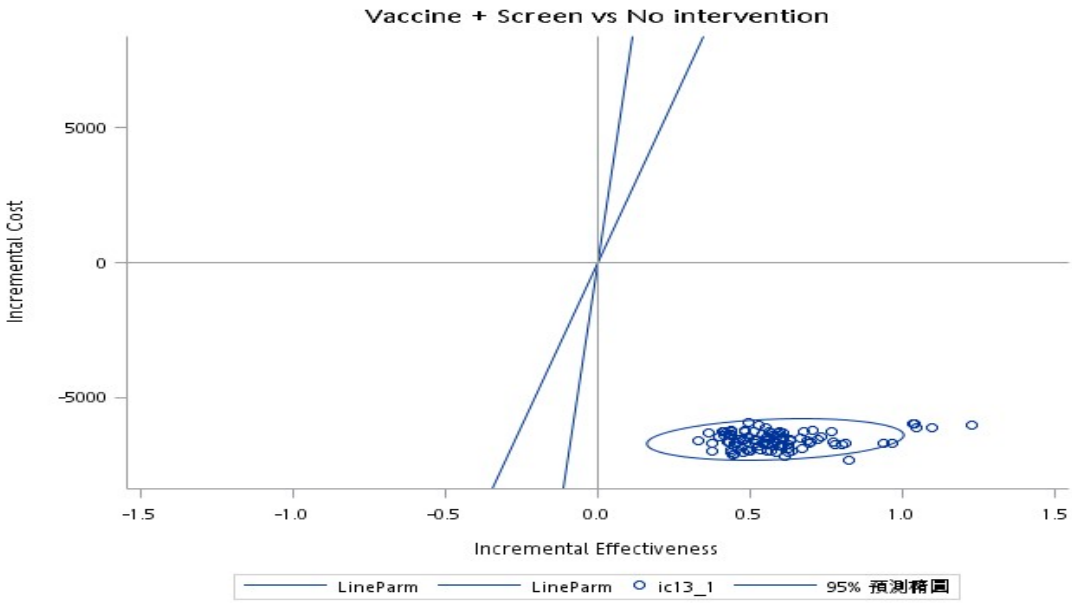
doi:10.6342/NTU201703133

Figure 5. 7 Scatter plot of incremental cost and incremental effectiveness for multiple modality of primary and secondary intervention for HCC compared to no intervention

(A) Universal Vaccination + Anti-viral therapy



(B) Universal Vaccination + Mass Screening



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(C) Universal Vaccination + Anti-viral therapy + Mass Screening

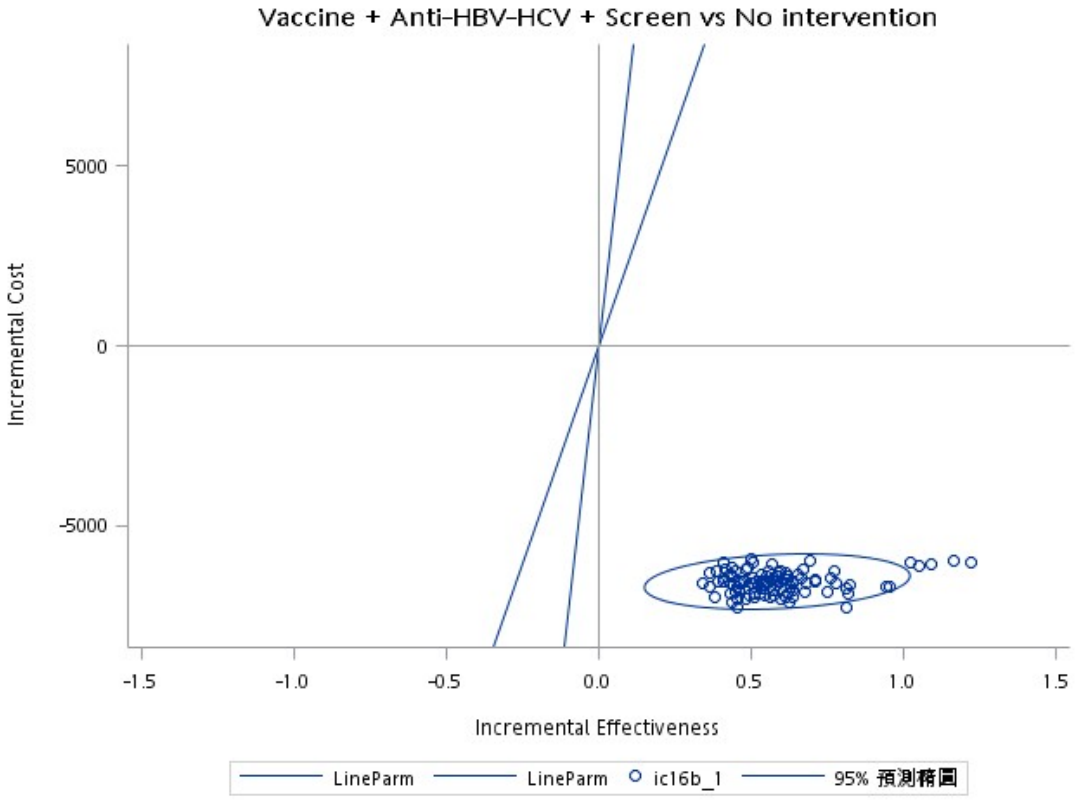

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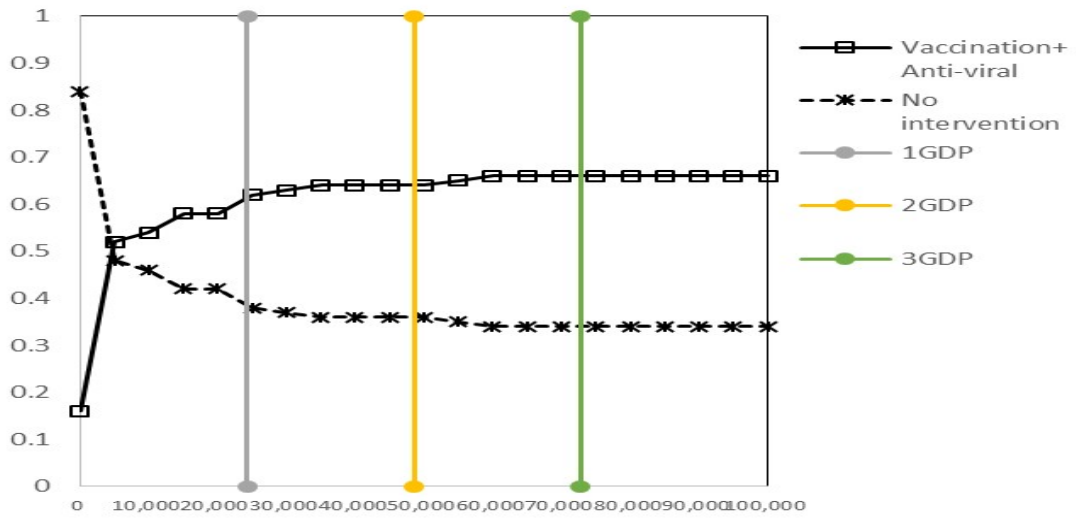
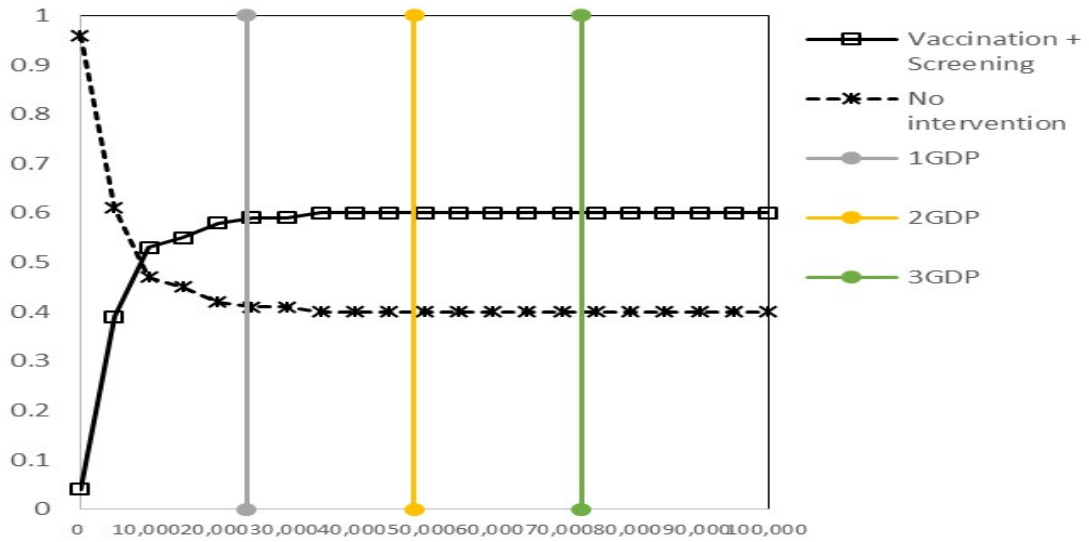
Figure 5. 8 Acceptability cures for preventing HCC with multiple modalities compared with given universal vaccination

(A) Vaccination + Anti-viral vs. No intervention

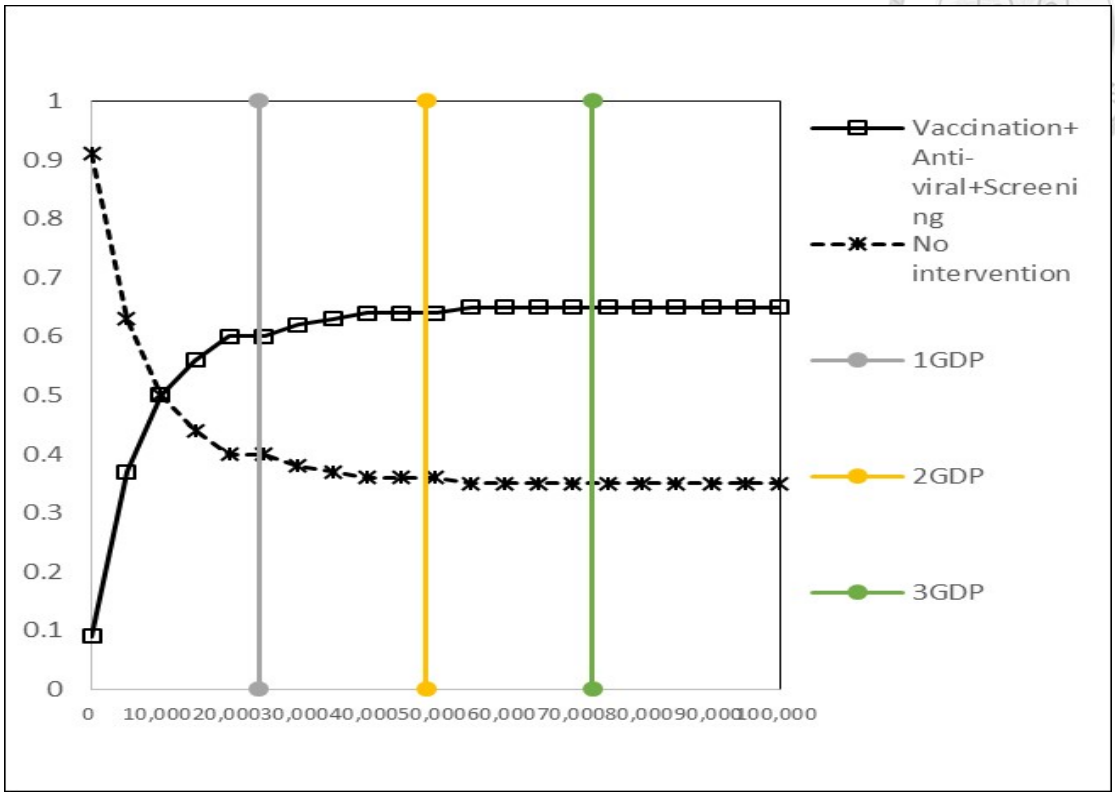


(B) Vaccination + Screening vs. No intervention



doi:10.6342/NTU201703133

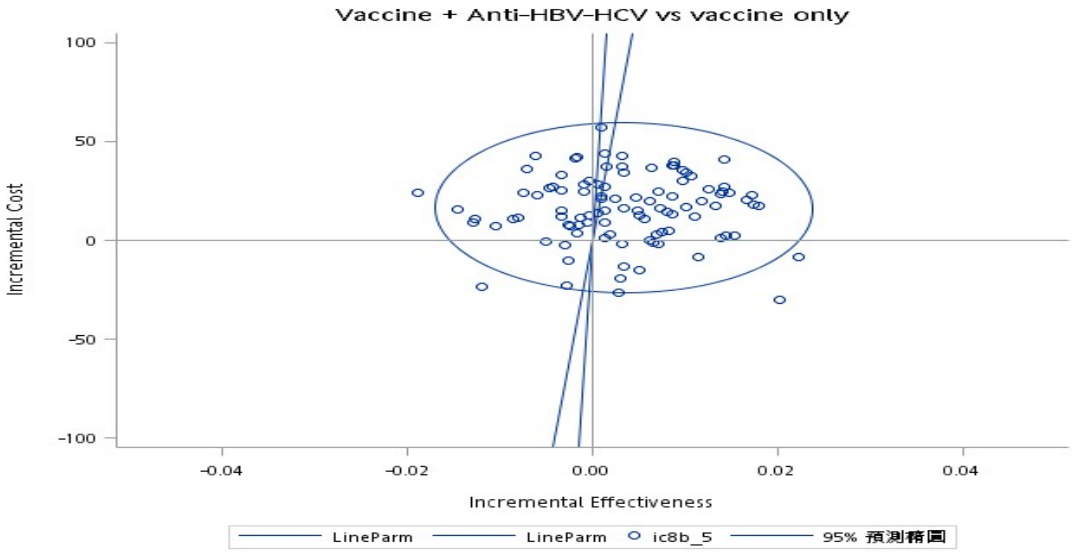
(C) Vaccination + Anti-viral + Screening vs. No intervention



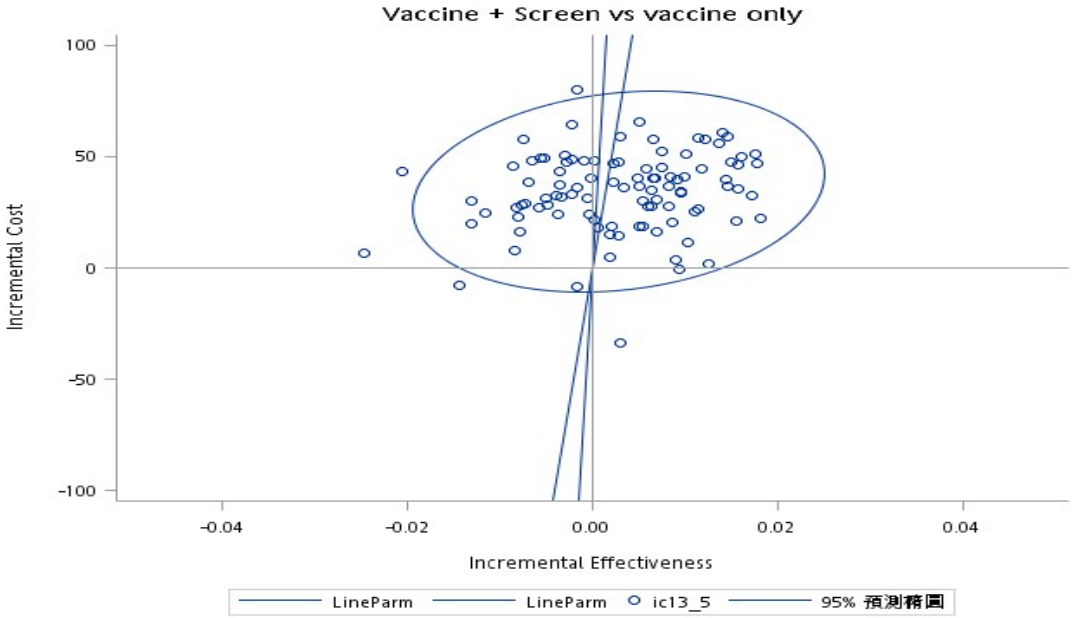
doi:10.6342/NTU201703133

Figure 5. 9 Scatter plot of incremental cost and incremental effectiveness for single modality of primary and secondary intervention for HCC compared to vaccination only

(A) Universal Vaccination + Anti-viral therapy

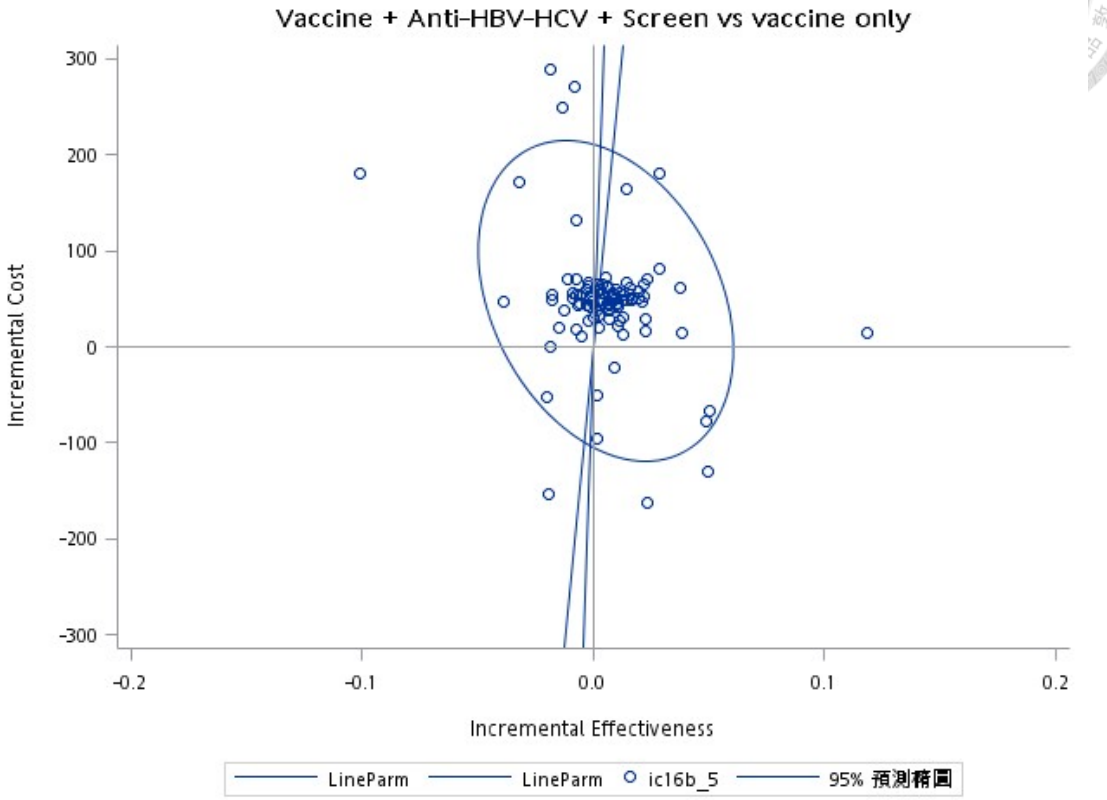


(B) Universal Vaccination + Mass Screening



doi:10.6342/NTU201703133

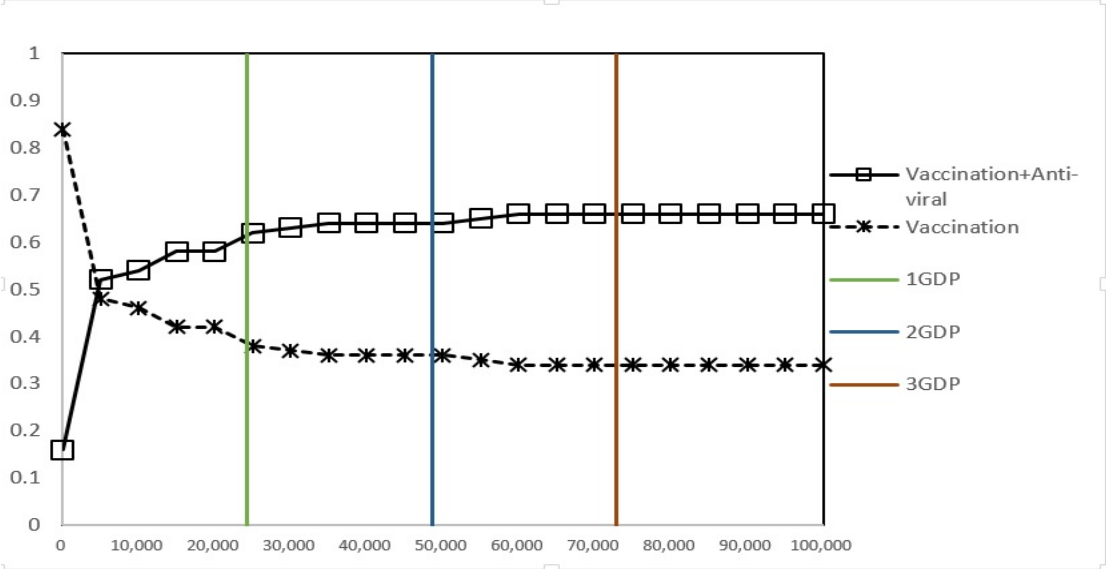
(C) Universal Vaccination + Anti-viral therapy + Mass Screening



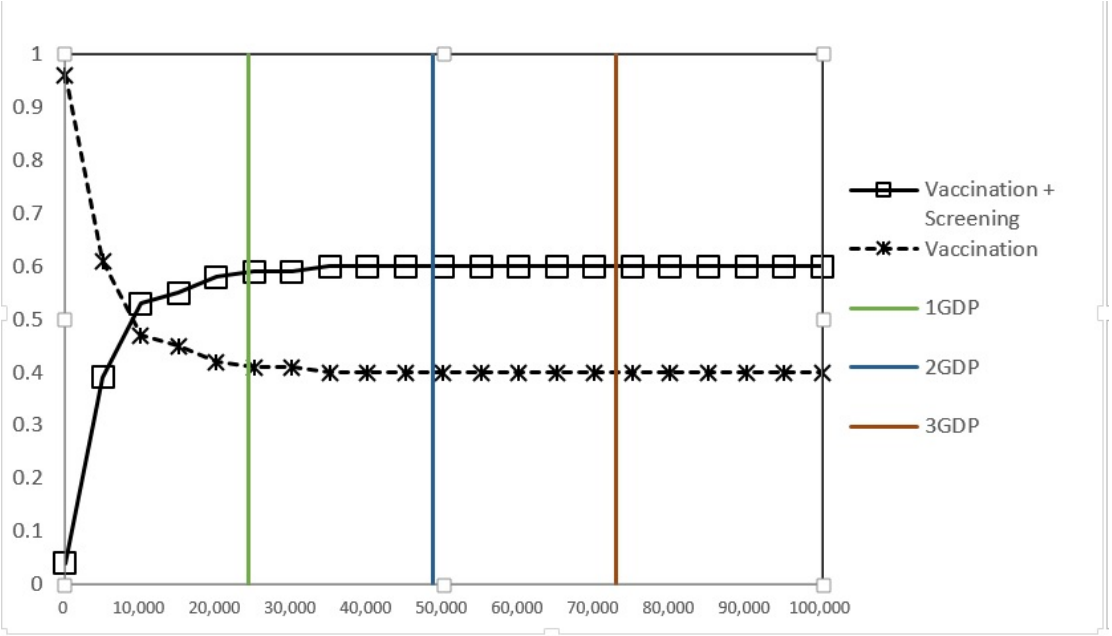
doi:10.6342/NTU201703133

Figure 5. 10 Acceptability cure with vaccination plus anti-viral therapy of mass screening for preventing HCC

(A) Vaccination + Anti-viral vs. vaccination



(B) Vaccination + Screening vs. Vaccination



doi:10.6342/NTU201703133

(C) Vaccination + Anti-viral + Screening vs. Vaccination

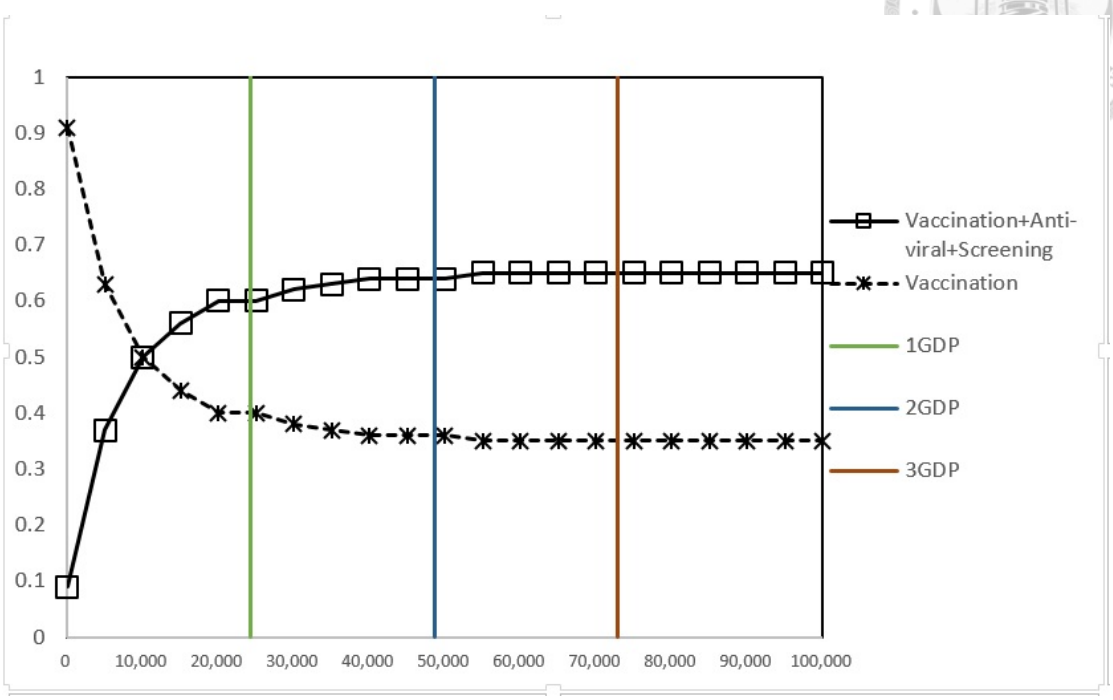


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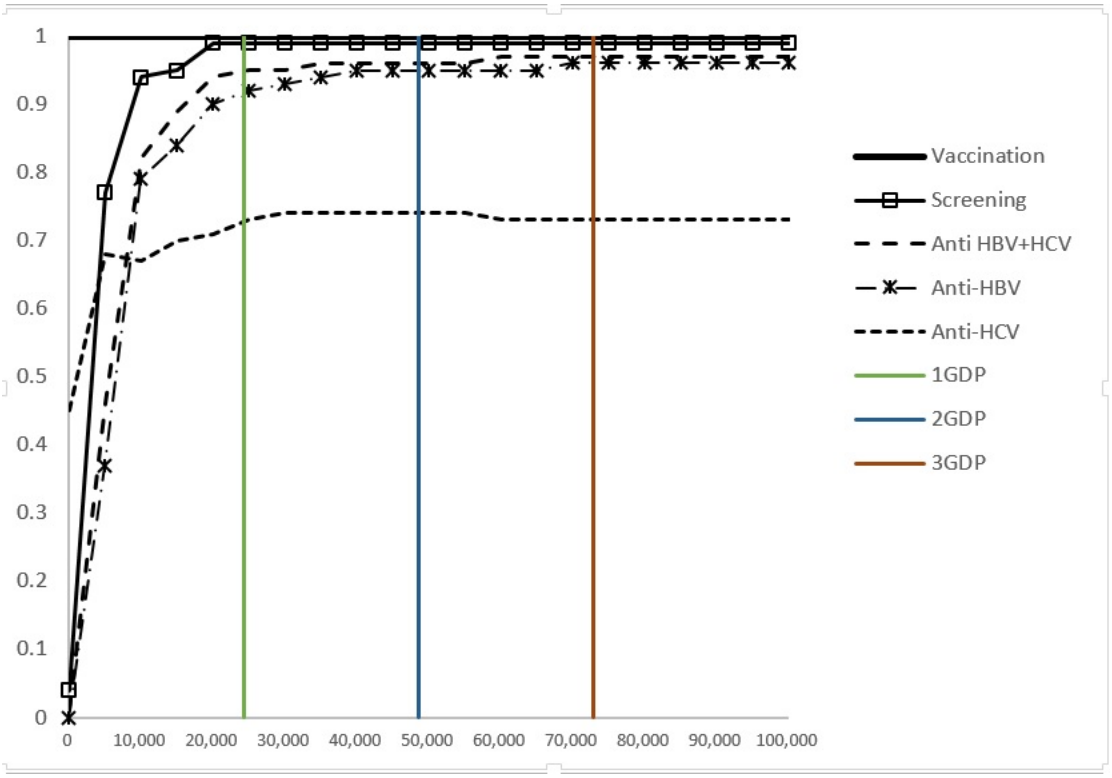
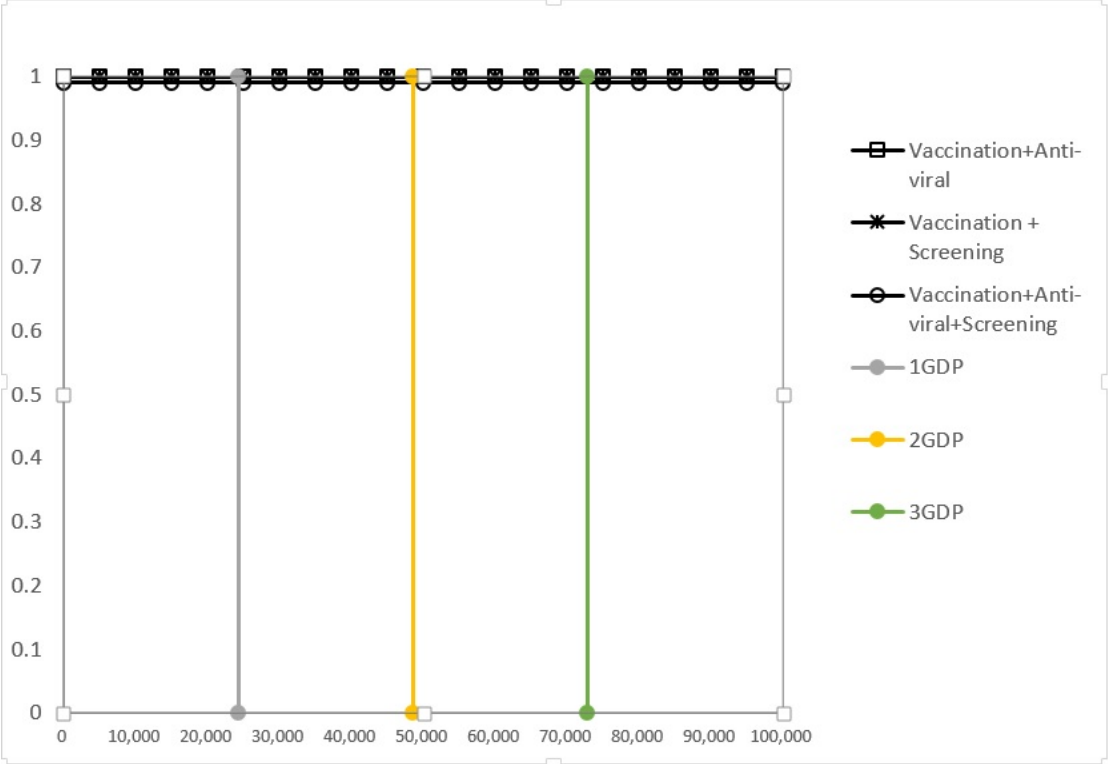
Figure 5. 11 Acceptability curve with single modality for preventing HCC vs. No intervention



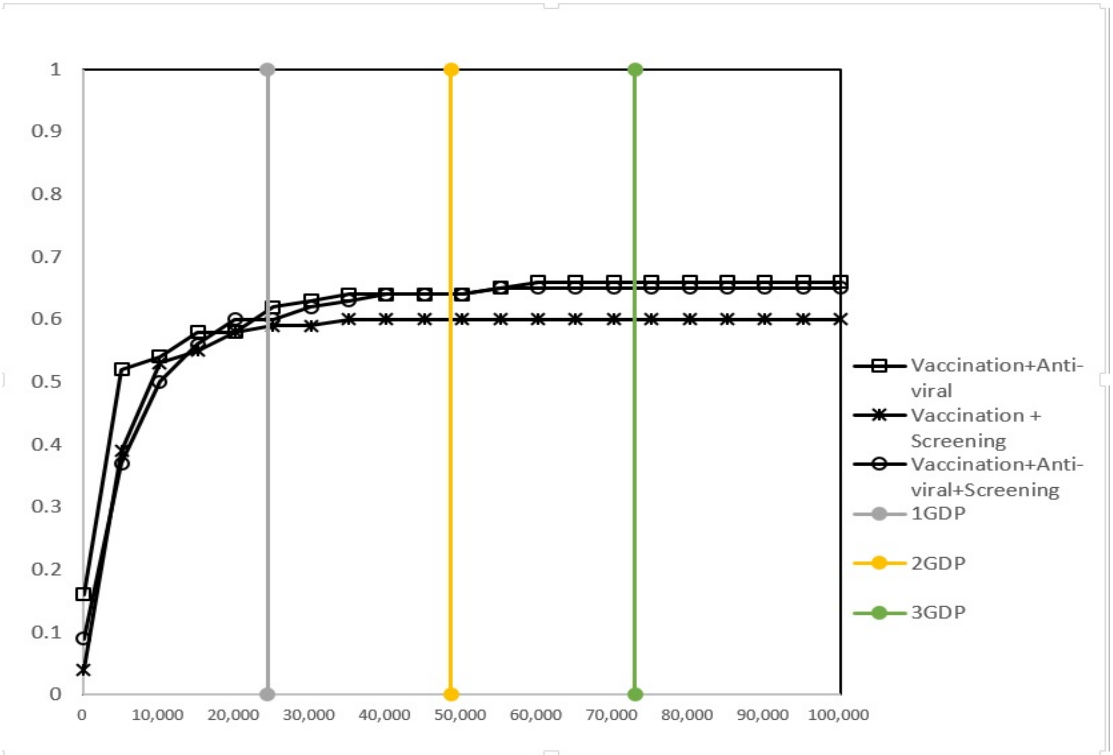
doi:10.6342/NTU201703133

Figure 5. 12 Acceptability curve with vaccination plus anti-viral therapy or mass screening for preventing HCC vs. no intervention



doi:10.6342/NTU201703133

Figure 5. 13 Acceptability curve with vaccination plus anti-viral therapy or mass screening for preventing HCC vs. vaccination



doi:10.6342/NTU201703133

Figure 5. 14 Scatter plot of incremental cost and incremental effectiveness for RFA and surgery among patients with small HCC

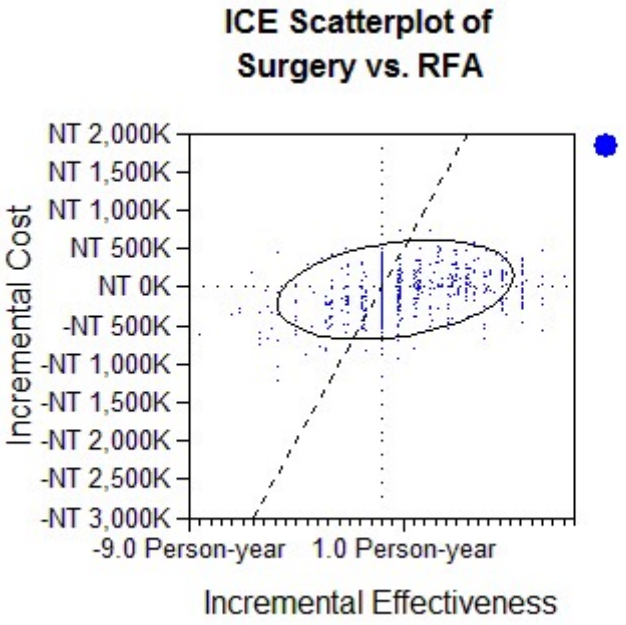


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Figure 5. 15 The incremental cost-effectiveness plot for the tertiary prevention for HCC among patients of chronic hepatitis C with SVR

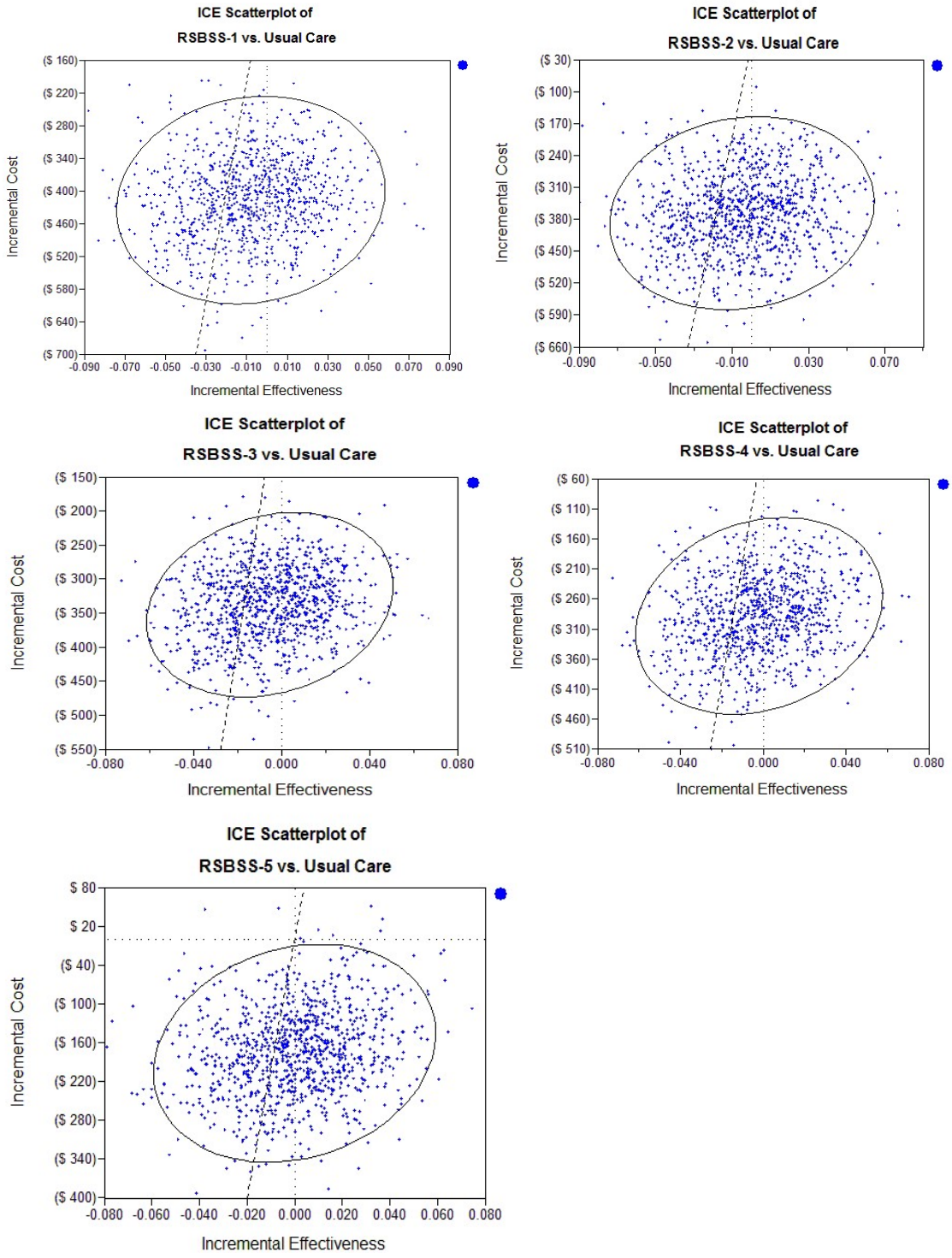

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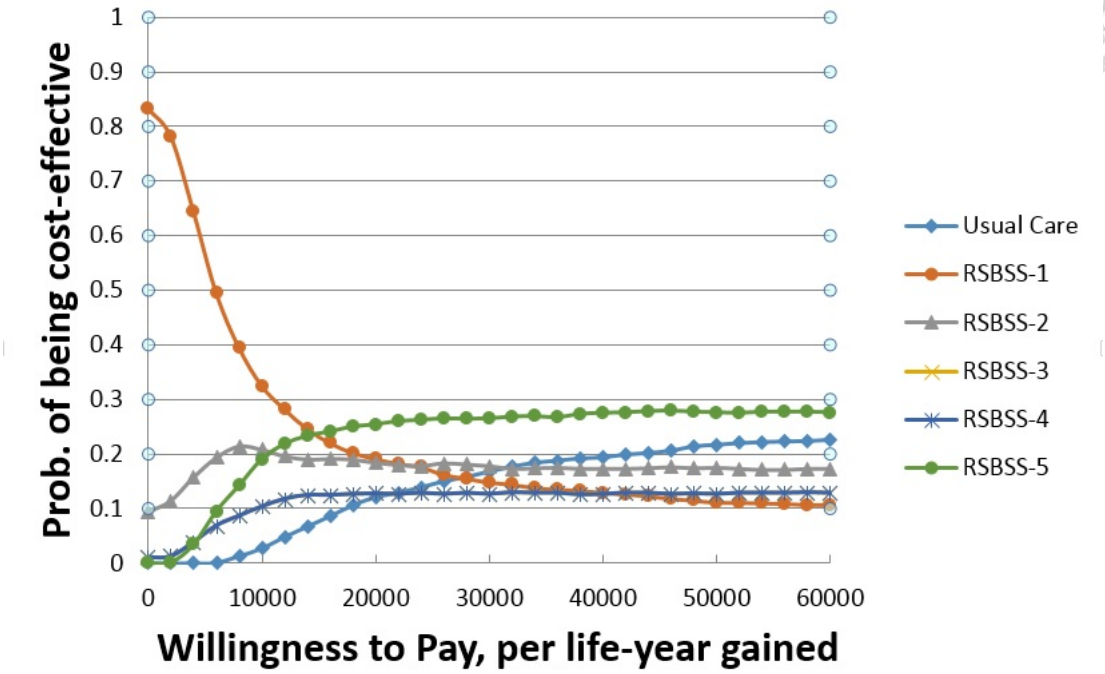
Figure 5. 16 The acceptability curve for the tertiary prevention for HCC among patients of chronic hepatitis C with SVR



RSBSS: risk stratification-based surveillance stratification

RSBSS-1: (High-risk group) 6-monthly；(Intermediate-risk group) 1-yearly；(Low-risk group) 2-yearly

RSBSS-2: (High-risk group) 3-monthly；(Intermediate-risk group) 1-yearly；(Low-risk group) 2-yearly

RSBSS-3: (High-risk group) 6-monthly；(Intermediate-risk group) 6-monthly；(Low-risk group) 2-yearly

RSBSS-4: (High-risk group) 3-monthly；(Intermediate-risk group) 6-monthly；(Low-risk group) 2-yearly

RSBSS-5: (High-risk group) 3-monthly；(Intermediate-risk group) 3-monthly；(Low-risk group) 1-yearly

doi:10.6342/NTU201703133

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